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Genetic Tests Under Incomplete Ascertainment

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GENETIC TESTS are commonly made without separation of the major sources of discrepancy, such as isolated cases and nonsegregating families. Often attention is directed toward estimation of the mean segregation frequency, rather than to specific tests of genetic hypotheses. This difference in emphasis is responsible for much computational difficulty, and therefore perhaps also for the failure of human geneticists to examine by stringent statistical methods the impressions obtained from family data. Only such tests can resolve discrepancies and discriminate among alternatives, such as phenocopies, mutations, and incomplete penetrance. Fortunately, it is possible by extension of existing formulae (Haldane, 1938, 1949; Finney 1949) and by use of maximum likelihood scores (Rao, 1952) to obtain simple and efficient tests of a variety of genetic hypotheses (Morton, 1958).

Definitions, assumptions, and methods

A *proband* is an affected person who at any time was detected independently of the other members of the family, and who would therefore be sufficient to assure selection of the family in the absence of other probands. The first proband detected in a family may be designated the index case, but the index case is no more important than the other probands, and valuable information will be lost if the total number of probands is not recorded. The term propositus will be avoided as ambiguous, since it has been used by some authors to signify the index case, and by others to include all probands. In a sibship of size s, it will be convenient to let a be the number of probands, b the number of affected children not probands, $a + b = r$, and $c = s - r$ be the number of normal children.

Families with no affected children, one affected child, and more than one affected child are called *nonsegregating*, *simplex*, and *multiplex*, respectively. An affected child is called *isolated* or *familial* in simplex and multiplex families, respectively. Isolated cases are of two possible types. *Chance* isolated cases are of the same origin as familial cases, and the other children in such families have the same *a priori* probability of being affected. *Sporadic* cases are of different origin from the familial and chance isolated cases (mutation, diagnostic error, phenocopy, etc.), and are assumed to be rare and independent, so that the probability is negligible that a familial case be of the same origin as a sporadic case.

Ascertainment may include both selection of families for analysis and recognition of segregating and nonsegregating families. *Complete selection* signifies random sampling of families *through the parents*, without consideration of the phenotypes of the

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children. ***Incomplete selection*** denotes selection of families ***through the children***, with exclusion of nonsegregating families. Five methods of ascertainment will be considered.

Complete selection

1. Separation of segregating and nonsegregating families, with failure to distinguish between homozygous and heterozygous parents in nonsegregating families. This separation is appropriate with dominant-recessive gene pairs when the parental genotypes can be inferred with certainty only in segregating families, for which it is equivalent to truncate selection (see below).

2. Separation of homozygous and heterozygous parents by direct inspection (for codominant gene pairs and rare "dominants" not selected through the children) or from information about the grandparents. In families of a given mating type and size, the distribution of the number of affected children is a complete binomial.

Incomplete selection

3. ***Truncate selection***, with random sampling of segregating families. Families with many affected children are no more likely to be selected than families with only one affected child, so that in sibships of a given mating type and size, the distribution of the number of affected children is a truncated binomial, with the first term missing. The phrase "complete selection of affected individuals" (Bailey, 1951) will be avoided as cumbersome and liable to confusion with complete selection (1 and 2 above).

4. ***Single selection***, with the probability of ascertainment so small that there is virtually no chance of having two probands in one sibship, and the probability that a family be ascertained is proportional to the number of affected children.

5. ***Multiple selection***, with a constant but arbitrary probability of ascertainment. The ascertainment probability π is the chance that an affected person be a proband. There may be from 1 to r probands in a family with r affected, and each proband may have $t \geq 1$ ascertainments. Multiple selection includes single and truncate selection as limiting cases.

In addition to the restrictions implicit in these definitions, the following assumptions are made.

1. The ascertainment probability π is constant, and all probands in a family are ascertained independently.

2. In multiplex and simplex families of the same origin, there is a constant *a priori* probability p that a child be affected (and the complementary probability $q = 1 - p$ that he not be affected).

3. Sporadic cases make up a proportion x of all cases in the population, and simplex families with sporadic cases constitute a proportion w of families of size s with affected children. Excluding sporadic cases, the mean number of affected children in a sibship of size s with at least one member affected is:

$$\bar{r} = \sum_{r=1}^{s} \frac{r \binom{s}{r} p^r q^{s-r}}{1 - q^s} = \frac{sp}{1 - q^s}$$

and

$$x = \frac{w}{w + (1 - w)\bar{f}}.$$

Substituting for $\bar{f}$ and rearranging,

$$w = \frac{xsp}{1 - q^s - x(1 - sp - q^s)}$$

If sporadic cases are not related to parity or parental age it may be shown that x is independent of s. For then the expected number of sporadic cases in a family of size s is $s\gamma$, and the expected number of nonsporadic cases is sf, where γ is the frequency of sporadic cases in the general population and f is the frequency of nonsporadic cases. Therefore the frequency of sporadic among all cases is $x = \gamma/(\gamma + f)$, which is independent of s. Since w increases with s, it is a less useful parameter than x. The condition for familial cases of sporadic origin to be negligible is $x\mu \ll (1 - x)\, p$, where μ is the probability of affection among sibs of sporadic cases. If the occurrence of sporadic cases is random among families, $\mu = \gamma$.

4. Let h be the probability that a parent be of genotype TT if his phenotype is the same as Tt. If mating is random and there are no sporadic cases ($x = 0$),

$$h = \frac{f_T^2}{f_T^2 + 2f_T f_t} = \frac{f_T}{f_T + 2f_t},$$

where f_T, f_t are the population gene frequencies of T, t. In a few cases involving multiple alleles, it will simplify the algebra to use h in a more general sense, as the probability that a parent either be homozygous, or that heterozygosity not be detectable because of the genotype of the other parent.

The distributions to be investigated arise from these assumptions and ancillary ones about p, π, x, and h. The null hypothesis specifies some theoretical value for p, and the other parameters either take theoretical values or are maximized subject to the hypothesis about p and the remaining parameters. For each independent observation, the maximum likelihood functions for any parameter, say θ, consist of a score whose expectation is zero on the null hypothesis,

$$u_\theta = \frac{\partial \ln L}{\partial \theta},$$

and its conditional variance, which is also the information about θ,

$$k_\theta = E\{u_\theta^2\} = -E\left\{\frac{\partial^2 \ln L}{\partial \theta^2}\right\}$$

where L is the probability of the observation, and u and k are evaluated at p_0, π_0, x_0, and h_0, the values of the parameters specified by the null hypothesis. Suppose the sample consists of m such observations and that none of the other parameters is estimated from the sample, and let $\Sigma u = U$ and $\Sigma k = K$. Then on the null hypothesis, U^2/K in the theory of large samples has the χ^2 distribution with one degree of free-

dom (testing the goodness of fit of θ_0), and, on the same assumptions, $\Sigma[u^2/k] - U^2/K$ has the χ^2 distribution with $m - 1$ degrees of freedom (testing homogeneity of θ). Furthermore, if the first χ^2 indicates a significant discrepancy, and this is thought not to be due to erroneous assumptions about other parameters, then θ may be estimated as

$$\theta^* = \theta_0 + U/K$$

with standard error $\sigma_{\theta^*} = \sqrt{1/K}$, if θ is constant, or approximately

$$s_{\theta^*} = \sigma_{\theta^*}\sqrt{\frac{\Sigma\left(\frac{u^2}{k}\right) - U^2/K}{m - 1}}$$

if θ varies among families. This is the first step in the iterative approach to the exact maximum likelihood solution, to which it is often a close approximation, (Rao, 1952, Chapter 4).

The above formulae may be generalized to the case where n parameters are to be estimated or tested against some null hypothesis. Let U_i be the total score for the i^{th} parameter, K_{ij} be the covariance between U_i and U_j, and K^{ij} be the corresponding element in the inverse matrix of the K_{ij}. Then to test a null hypothesis with respect to n parameters,

$$\chi^2_n = \sum_{i,j=1}^{n} U_i U_j K^{ij} = \sum_{i=1}^{n} U_i^2 K^{ii} + 2\sum_{i<j} U_i U_j K^{ij}.$$

To test homogeneity of θ_i, assuming homogeneity of $n - 1$ other parameters estimated from the sample, $\chi^2_{m-n} = \Sigma(u_i^2/k_i) - U_i^2/K_{ii}$. To estimate the i^{th} parameter θ_i from an initial estimate θ_{0i}, $\theta_i^* = \theta_{0i} + \sum_{j=1}^{n} U_j K^{ij}$, omitting from the original K_{ij} matrix any parameters not estimated from the sample. The standard error of this estimate is $\sigma^*_{\theta i} = \sqrt{K^{ii}}$ if θ_i is constant and the assumptions about the other parameters are correct. If any parameter is heterogeneous, an empirical standard error for θ_i is $s_{\theta^* i} = \sqrt{\chi^2/(m - n)}$ (Rao, 1952, Chapter 4).

This empirical standard error is approximate in two ways: it is an estimate of the actual sampling error, to which it converges in large samples; with heterogeneity in θ_i, the maximum likelihood (M.L.) estimate is not necessarily unbiased, even in the limit for large samples, but converges to some other value different from, although usually near, the mean value $E(\theta_i)$. If the data cannot be separated into homogeneous groups, this bias is unavoidable, and the M.L. estimate is as satisfactory as any other.

The appendix gives formulae for the five modes of ascertainment. Where appropriate, each family is scored as five independent observations, corresponding to:

1. Separation of segregating and nonsegregating families.
2. Among segregating families, separation of simplex and multiplex families.
3. Among multiplex families, the distribution of r.
4. Among multiplex families under multiple selection, the distribution of probands among r affected.
5. Among probands, the distribution of t ascertainments.

Tests of homogeneity among these sources will detect discrepancies obscured in the pooled data and help to identify disturbing factors. Homogeneous data may always be pooled, since the scores and variances are additive and jointly exhaust the information in the sample, providing a fully efficient analysis in the neighborhood of the null hypothesis.

Incomplete ascertainment

It has been assumed that π is constant and ascertainments are independent. However, human data may depart from this model in several ways, which may be distinguished by a test of homogeneity of estimates of π from ascertainments, probands, and affected children.

1. Ascertainments may not be independent, because referral from one source favors or precludes referral from another. If this cannot be avoided by careful definition of the sources of ascertainment, the method of §7 in the appendix will not be applicable to the distribution of the number of ascertainments. However, probands will still give valid information, if the probability that an affected individual be a proband is independent of the number of his affected sibs, the severity of their affection, and the number of other probands in the family.

2. The probands may not be correctly identified, either through failure to record probands after the index case or through counting as probands sibs who were in fact ascertained from other family members. When this is the only discrepancy from the ascertainment model, the analysis will be valid if the number of probands is neglected, and π estimated solely from the distribution of r in segregating families. However, much of the genetic information is lost if probands and ascertainments are not identified.

3. If a trait is more likely to be correctly diagnosed when it is familial, then isolated cases will be poorly or excessively represented. The analysis may be restricted to multiplex families.

4. The number of ascertainments (t) may be known even if the number of probands has been recorded incompletely or not at all. Providing ascertainments are independent, the method of §7 of the appendix may still be used.

5. The probability of ascertainment may be heterogeneous among families because the trait is a mixture of entities, which as far as possible should be separated before the analysis proceeds.

6. The ascertainment model may be systematically wrong if the cases are collected from occasional reports in the literature or other biased sources. In this event it is still possible that the distribution of r among segregating families, or at least among multiplex families, may be adequately described by some effective ascertainment probability π, and that a valid analysis of p may be carried out from the empirical standard error.

Obviously any test on p, x, h, or π depends on the accuracy of the ascertainment model. Unfortunately, analysis of incomplete ascertainment in the past has been so inadequate, that the magnitude of the error of this method cannot be assessed. However, it is hopeful that even data from the medical literature seem to fit fairly well for albinism (Haldane, 1949), and there is reason to suppose that a more sys-

tematic collection of cases would in general conform more closely to the ascertainment model of this paper.

Incomplete penetrance and delayed onset

The assumption that p is constant neglects interfamily heterogeneity in penetrance and age at onset. In this case the analysis will be approximate, but the use of an empirical standard error helps to protect against invalid conclusions.

For a common trait, incomplete penetrance so complicates the analysis that the methods of this paper are not always applicable, since several segregation ratios will occur within some phenotypic mating classes. However, if a trait is rare enough so that nearly all segregating matings are of one type, the analysis presents no difficulty. The expected segregation frequency will then be the product of the theoretical value p_0 and the average penetrance for the sample (y).

Delayed onset constitutes an important special case of incomplete penetrance. Let f(z) be the frequency of age z at death or last examination among normal and affected siblings, $f_1(z)$ be this frequency with the index cases excluded, and G(z) be the cumulative frequency of onset at age z among affected cases. Then if incomplete penetrance is entirely due to delayed onset, the estimate of the average penetrance in the sample is $y = \int f(z)G(z)dz$ for complete selection and $\int f_1(z)G(z)dz$ for single selection, where integration is over the range of z. Since these are the two limiting cases, the best estimate of y should lie between these values.

As with ascertainment, it is not clear how adequate this model for the segregation ratio will be. Reliable results may be expected if the data are homogeneous. However, the assumption of incomplete penetrance is so consistent with variable p, that it might in practice be difficult to recognize other kinds of heterogeneity. Only actual trial of these methods will determine their limits, but the more regular the sampling procedure and the higher the penetrance, the greater their precision will be.

An example of complete selection

Taylor and Prior (1938) and Race and others (1942) presented a series of 236 families tested for the A_1A_2BO blood group factors, and analyzed them by partition into segregating and nonsegregating families. Pooling reciprocals, there are 21 different mating types, in six of which there is no dominance and separation of homozygous and heterozygous parents is by direct inspection. The progeny distributions in the 15 remaining types give 28 degrees of freedom for tests of genetic hypotheses by calculation of expected numbers of families.

If we separate parental segregations where possible, and apply the methods of the present paper, there are only six segregation types, in two of which there is no dominance (h = 0). Considering backcrosses and intercrosses separately, there are eleven mating types, which require calculation of only four values of h (table 1). Letting p_1, p_2, q and r denote the gene frequencies of A_1, A_2, B, and O, respectively, and using the estimates of Ikin, Prior, Race, and Taylor (1939) from an English sample of 3,459 persons, the values of h are computed as follows:

Type 1. The probability that an A_1 parent is A_1A_1 and not A_1O or A_1A_2 is $h = p_1/[p_1 + 2(p_2 + r)] = .1252$

TABLE 1. CLASSIFICATION OF ABO MATINGS

Segregation type			Backcross	Segregants		Intercross
	T	t		T	t	
1	A_1	$A_2 + O$	$A_1 \times O$	A_1	A_2, O	$A_1 \times A_1$
			$\times A_2$	A_1	A_2, O	
			$\times B$	A_1, A_1B	B, A_2B, O	
			$\times A_2B$	A_1, A_1B	B, A_2B	
			$\times A_1B$ exclude non-B progeny	A_1B	A_2B, B	
2	A_1	B	$A_1B \times O$	A_1	B	$A_1B \times A_1B$
			$\times A_2$	A_1	A_2B, B	
			$\times B$	A_1, A_1B	B	
			$\times A_2B$	A_1, A_1B	A_2B, B	
			$\times A_1$	A_1	B, A_2B, A_1B	
3	A_2	O	$A_2 \times O$	A_2	O	$A_2 \times A_2$
			$\times B$	A_2, A_2B	B, O	
			$\times A_2B$ exclude non-B progeny	A_2B	B	
			$\times A_1B$ exclude non-B progeny	A_2B	B	
4	A_2	O	$A_2 \times A_1$ exclude A_1 progeny	A_2	O	
5	A_2	B	$A_2B \times O$	A_2	B	$A_2B \times A_2B$
			$\times B$	A_2B, A_2	B	
			$\times A_1B$	A_1, A_2B	A_1B, B	
			$\times A_1$	A_1, A_2	A_1B, B, A_2B	
			$\times A_2$	A_2	A_2B, B	
6	B	O	$B \times O$	B	O	$B \times B$
			$\times A_1B$ exclude B progeny	A_1B	A_1	
			$\times A_2B$ exclude B progeny	A_2B	A_2	
			$\times A_1$	A_2B, A_1B, B	A_1, O, A_2	
			$\times A_2$	A_2B, B	O, A_2	

Type 3. The probability that an A_2 parent is A_2A_2 and not A_2O is $h = p_2/(p_2 + 2r) = .0501$

Type 4. The probability that an A_2 parent is A_2A_2 and not A_2O, *or* that the non-A_1 allele of a heterozygous A_1 parent is A_2 and not O, is

$$h = 1 - \{2r/(p_2 + 2r)\}\{r/(p_1 + r)\} = .1407.$$

This is a case where multiple allelism makes it convenient to define h, not as the probability of homozygosity, but as the probability either of homozygosity or of heterozygosity not detectable because of the genotype of the other parent. This

mating is treated as a backcross, because segregation of the A_1 parent is eliminated by exclusion of A_1 progeny.

Type 6. The probability that a B parent be BB and not BO is $h = q/(q + 2r) = .0443$

In applying these formulae, the relationship of some parents *inter se* has been ignored, which has the effect of exaggerating deviations from the null hypothesis. Since all tests are in excellent agreement with hypothesis, no more elaborate treatment is required.

Table 2 summarizes the results. Only nine of the eleven possible mating types occur in these data. The frequencies of segregating and nonsegregating families agree well with the values of h calculated from the English gene frequency estimates on the assumption of random mating and negligible selection, as shown by the analyses of both p and h.

In the analyses of segregating families, types 3 and 4 are pooled, but type 1 is divided into A_1/O and A_1/A_2 segregations. This gives six possible segregation types, or 13 mating types when intercrosses and backcrosses are distinguished, of which nine are observed in these data. Agreement with hypothesis is again excellent.

It is noteworthy that the partition into segregating and nonsegregating families gives only 743 of the total of 1724 units of genetic information in these data, or 43 per cent, while the analysis of segregating families accounts for the remaining 57 per cent. Much of the value of laboriously collected data will be lost unless both sources of information are utilized.

The application of these methods to tests on reciprocal crosses and other matings within a segregation type is obvious.

TABLE 2. ABO DATA

Source	Analysis of p		
	Σk_{pp}	d.f.	χ^2
1) r = 0 vs. r > 0	743		
Mating types		9	5.11
Families within types		210	214
2) r = 1 vs. r > 1	603		
Mating types		9	12.53
Families within types		103	106
3) r among r > 0	378		
Mating types		6	7.63
Families within types		35	38
Total	1724		
Mating types		9	9.92
Families within types		210	236
	Analysis of h		
		d.f.	χ^2
Mating types		9	3.20
Families within types		210	216
$\Sigma k_{hh} = 969$			

DISCUSSION

There have been four stages in the development of segregation analysis in man. At first, tests of significance based on complete selection were applied to rare dominant pedigrees and later to codominant factors. Next, the disturbing effects of truncate selection were recognized, leading to the development of the *a priori* methods of Bernstein, Lenz, and others, and the *a posteriori* method of Haldane. (The methods of the present paper are *a priori* in the sense of starting with a test of some null hypothesis, but *a posteriori* in leading by iteration to the maximum likelihood estimate if the null hypothesis is rejected.) Thirdly, multiple selection was considered by Weinberg in the proband method, which is not fully efficient except in the limiting case of single selection, and more elaborately by later authors, none of whom used the large amount of information present in the number of ascertainments of probands.

Finally, interest in mutation and other sources of sporadic cases led to their inclusion in the general models of this paper, with separation from incomplete penetrance and other superficially similar phenomena. It seems remarkable that this generalization should have required half a century. This is perhaps understandable considering the small number of workers in formal human genetics and the greatly increased concern with sporadic cases in recent years in connection with mutation studies. However, a more cogent reason may be found in the development of adequate computing equipment.

Ten years ago, a geneticist might well have been discouraged by the equations of the present paper, requiring many days or weeks of desk calculation for their application. Fortunately, readily available computers have reduced this time by a factor of 100 or more, with incorporation of computing checks that insure accuracy. Once programmed, very little labor is required to tabulate scores for various values of the parameters and to perform the same type of analysis on other data. All of the methods of this paper, with others reported elsewhere (Morton, 1958) or still unpublished, have been programmed for the IBM 650 computer, checked exhaustively, and employed in many analyses. This program, written by Mr. R. A. Hedberg and Mrs. Nancy Jones, may be used by arrangement with the Department of Medical Genetics, University of Wisconsin Medical School.

Two special applications of these methods are of interest. The sometimes complex analysis of concordance in twins may be assimilated by considering each set of twins as a sibship of size 2, and similarly each set of triplets as a sibship of size 3, etc., where p is the concordance. The formulae may be used, with some extension (also programmed for the IBM 650), to distinguish between technical errors, illegitimacy, and disturbed segregation in the blood group systems.

These procedures, in studies to be published shortly, give remarkably good agreement with genetic theory and other sources of information. The apprehension expressed by Kempthorne (1957, p. 195), that segregation data in man are so complicated by family planning and other disturbances as not to be amenable to precise analysis by simple models, appears to be unfounded.

SUMMARY

Methods are developed for analysis of data with arbitrary segregation ratio, ascertainment frequency, and incidence of sporadic cases, with separation of mutations, phenocopies, and incomplete penetrance. Tests of consistency and estimates by maximum likelihood scores are provided for all parameters. Formulae and an example are given. The methods are also applicable to estimation of concordance in twins and natural selection in families.

APPENDIX. DERIVATION OF FORMULAE

1. *Separation of segregating and nonsegregating families. Complete selection, complete penetrance, no sporadic cases.*

The most important matings are possible backcrosses ($p_0 = \frac{1}{2}$) and diallelic intercrosses ($p_0 = \frac{1}{4}$). Possible multiple allelic intercrosses may be scored as backcrosses for each parent separately unless the parental phenotypes are identical, but only informative progeny should be scored. Thus if T_1 is dominant to t_2 and both dominant to t, then in matings of type $T_1- \times t_2-$ all s children may be scored for the T_1 parent, but only non-T_1 children for the t_2 parent, with

$$h = f_{T_1}^2/(f_{T_1}^2 + 2f_{T_1}f_{t_2} + 2f_{T_1}f_t) = f_{T_1}/[f_{T_1} + 2(f_{t_2} + f_t)]$$

in the first case, and $h = 1 - \{2f_t/(f_{t_2} + 2f_t)\}\{f_t/(f_t + f_{t_2})\}$ in the second, since segregation of the t_2- parent can be recognized only if the non-T_1 allele of a heterozygous T_1- parent is t. The same principles apply to analysis of other modes of selection.

In possible backcrosses of size s, the probability of a segregating family is $m = (1 - h)(1 - q^s)$, and $u_p = \dfrac{\partial (\ln m)}{\partial p} = \dfrac{1}{m}\dfrac{\partial m}{\partial p} = sq^{s-1}/(1 - q^s)$, similarly $u_h = \dfrac{1}{m}\dfrac{\partial m}{\partial h} = -1/(1 - h)$. The probability of a nonsegregating family $= 1 - m = h + (1 - h)q^s$, and $u_p = -(1 - h)\,sq^{s-1}/[h + (1 - h)q^s]$, $u_h = (1 - q^s)/[h + (1 - h)q^s]$. The conditional variances and covariance are

$$k_{pp} = \frac{1}{m}\left(\frac{\partial m}{\partial p}\right)^2 + \frac{1}{1 - m}\left(\frac{\partial(1 - m)}{\partial p}\right)^2 = (1 - h)s^2q^{2s-2}/(1 - q^s)[h + (1 - h)q^s],$$

$$k_{hh} = \frac{1}{m}\left(\frac{\partial m}{\partial h}\right)^2 + \frac{1}{1 - m}\left(\frac{\partial(1 - m)}{\partial h}\right)^2 = (1 - q^s)/(1 - h)[h + (1 - h)q^s],$$

and

$$k_{hp} = \frac{1}{m}\frac{\partial m}{\partial p}\frac{\partial m}{\partial h} + \frac{1}{1 - m}\frac{\partial(1 - m)}{\partial p}\frac{\partial(1 - m)}{\partial h} = -sq^{s-1}/[h + (1 - h)q^s].$$

In possible intercrosses, the probability of a segregating family is $(1 - h)^2(1 - q^s)$, and $u_p = sq^{s-1}/(1 - q^s)$, $u_h = -2/(1 - h)$. The probability of a nonsegregating

family is $1 - (1 - h)^2(1 - q^s)$, and $u_p = -(1 - h)^2sq^{s-1}/\{1 - (1 - h)^2(1 - q^s)\}$, $u_h = 2(1 - h)(1 - q^s)/\{1 - (1 - h)^2(1 - q^s)\}$. The conditional variances and covariance are

$$k_{pp} = (1 - h)^2s^2q^{2s-2}/(1 - q^s)\{1 - (1 - h)^2(1 - q^s)\},$$
$$k_{hh} = 4(1 - q^s)/\{1 - (1 - h)^2(1 - q^s)\},$$
and $$k_{hp} = -2(1 - h)sq^{s-1}/\{1 - (1 - h)^2(1 - q^s)\}.$$

The parents of these sibships and unrelated individuals from the same population contribute other information about h. For the estimate of h from the gene frequencies f_T and f_t, $k_{hh} = (2f_t + f_T)^4/4\{f_t^2 \text{ var } (f_T) + f_T^2 \text{ var } (f_t) - 2f_Tf_t \text{ cov } (f_t, f_T)\}$. When $f_T = 1 - f_t$, this reduces to $k_{hh} = (1 + f_t)^4/4 \text{ var } (f_t)$. The sources of information about h are possible backcrosses, possible intercrosses, the parents, and the population sample, giving three degrees of freedom for testing homogeneity of h. Three cases arise.

Case 1. Homogeneous h, with the value of k_{hh} in the population sample much larger than the sum of the backcross and intercross values. Sampling error in h may be neglected. This is the method for a preliminary analysis, more refined tests being necessary only if there is an apparent deviation from the null hypothesis.

Case 2. Homogeneous h, the sampling error of h not negligible. The values of k_{hh} may be pooled, but the other scores are kept separate and the scores from backcrosses and intercrosses distinguished by 1 and 2 respectively. Then the scores and information matrix evaluated at p_{01}, p_{02}, and h give the required estimates and their variances.

Case 3. Heterogeneous h. This may arise from chance, incorrect gene frequencies, nonrandom mating, or disturbed segregation. These hypotheses can be examined separately by comparison of the parental distribution with the population sample, a contingency test of random association of parental phenotypes, and by tests on the segregating families (§3). If desired, h may be estimated as above on the evidence of the children and parents alone.

2. *Separation of homozygous and heterozygous parents. Complete selection.*

Since segregation is not necessary for recognition of parental heterozygosity, all heterozygous parents are scored. The two important segregation ratios are 1:1 and 1:2:1, the latter being reduced to the former by comparing the two classes of homozygotes, then the pooled homozygotes with the heterozygotes. If there are no sporadic cases ($x = 0$), the distribution of r affected is $\binom{s}{r}p^rq^{s-r}$, and $u_p = r/p - (s - r)/q = r/pq - s/q$. Let $e = s/q$, so that $u_p = r/pq - e$. Clearly e is the expected value of r/pq on the null hypothesis. To obtain k_{pp}, note that

$$E(r/pq)^2 = E\{r(r - 1)\}/p^2q^2 + e/pq.$$

Substituting $s(s - 1)p^2$ for $Er(r - 1)$ we obtain: $s(s - 1)/q^2 + s/pq^2$, so that $k_{pp} = E(r/pq)^2 - e^2 = s/pq$.

This anticipated result required no derivation, but illustrates a method that will be used later for related distributions. The scores, although not needed in the analysis of this type of selection, are convenient for combination of these families with other

data. If desired, each family may be partitioned into several items of information, the first corresponding to comparison of segregating and nonsegregating families and obtained as in the last section with $h = 0$. The analysis of segregating families proceeds as for truncate selection.

If there are nongenetic sporadic cases ($x > 0$), the most important matings with this method of ascertainment are possible backcrosses in which the affected parent is a proband and may be a phenocopy. Neglecting the possibility of two phenocopies or of a phenocopy and a genetic case in the same family, the probability of a segregating family is $(1 - x)(1 - q^s)$, and of a nonsegregating family is $x + (1 - x)q^s$. The scores and variances for x and p may be obtained as in the last section by substituting x for h. The analysis of segregating families is given in the next section.

3. *Truncate selection* ($\pi = 1$).

With the type of selection the distribution of r affected ($r > 0$) when $x = 0$ is $\binom{s}{r}p^r q^{s-r}/(1 - q^s)$, and $u_p = r/pq - e$, where $e = s/q(1 - q^s)$. We find $k_{pp} = s(s - 1)/q^2(1 - q^s) + e/pq - e^2 = s(1 - q^s - spq^{s-1})/pq(1 - q^s)^2$. Values of k have been tabulated by Finney (1949), who used the symbol W. However his "bias" B is not the same as our e, being equal to $e - kp$.

These values of u and k give an omnibus test of the null hypothesis that $x = 0$, $\pi = 1$, and $p = p_0$. More specific tests may be obtained from the separation of simplex and multiplex families and the distribution of r within multiplex families. The scores u_p and u_x and their conditional variances and covariance may be found in §5 for $\pi = 1$.

4. *Single selection* ($\pi \to 0$).

The probability of selection of a family with r affected is $\lim_{\pi \to 0} \{1 - (1 - \pi)^r\} = r\pi$, and when $x = 0$ the probability of selection of a family of size s is $\Sigma\binom{s}{r}\pi r p^r q^{s-r} = sp\pi = \lim_{\pi \to 0} \{1 - (1 - p\pi)^s\}$. Therefore the distribution of r affected in families of size s is $r\pi\binom{s}{r}p^r q^{s-r}/sp\pi = \binom{s-1}{r-1}p^{r-1}q^{s-r}$, and single selection is equivalent to complete selection of the siblings of the index case.

With x arbitrary, the siblings give a family test of the sporadic or nonsporadic origin of the index case, and the frequency of simplex families is $x + (1 - x)q^{s-1}$. The scores u_x and u_p with their variances k_{xx} and k_{pp} and the covariance k_{xp} may be obtained as for possible backcrosses in §1 by substituting λ for h and $s - 1$ for s. In multiplex families, the distribution of $r - 1$ affected among the $s - 1$ siblings of the index case is scored as for truncate selection ($r - 1 > 0$).

5. *Multiple selection* ($0 < \pi \leqq 1$).

When $x = 0$, the distribution of r affected is

$$\binom{s}{r}p^r q^{s-r}\{1 - (1 - \pi)^r\}/\{1 - (1 - p\pi)^s\},$$

since $\Sigma\binom{s}{r}p^r q^{s-r}(1 - \pi)^r = (1 - p\pi)^s$.

With x arbitrary, the frequency of simplex families is

$$m_1 = C\pi\{w + (1 - w)spq^{s-1}/(1 - q^s)\},$$

and the frequency of multiplex families is

$$m_2 = C(1 - w)\{1 - (1 - p\pi)^s - sp\pi q^{s-1}\}/(1 - q^s),$$

where C is a constant such that $m_1 + m_2 = 1$. We find

$$C = 1/\{w\pi + (1 - w)[1 - (1 - p\pi)^s]/(1 - q^s)\}.$$

Substituting for w,

$$m_1 = \frac{sp\pi\{x + (1 - x)q^{s-1}\}}{xsp\pi + (1 - x)\{1 - (1 - p\pi)^s\}} = sp\pi A/B,$$

say, and the scores for simplex families are

$$u_x = (BW - AY)/AB, \qquad u_\pi = (B - sp\pi Z)/\pi B,$$

and $u_p = (BX - sp\pi AZ)/pAB$, where

$$W = 1 - q^{s-1} \qquad Y = sp\pi - 1 + (1 - p\pi)^s$$

$$X = x + (1 - x)q^{s-1} - p(1 - x)(s - 1)q^{s-2} \qquad Z = x + (1 - x)(1 - p\pi)^{s-1}.$$

Similarly,

$$m_2 = \frac{(1 - x)\{1 - (1 - p\pi)^s - \pi spq^{s-1}\}}{xsp\pi + (1 - x)\{1 - (1 - p\pi)^s\}} = (1 - x)D/B,$$

say, and the scores for multiplex families are $u_x = -\{(1 - x)Y + B\}/(1 - x)B$, $u_\pi = sp(BJ - DZ)/BD$, and $u_p = s\pi(BK - DZ)/BD$, where

$$J = (1 - p\pi)^{s-1} - q^{s-1} \qquad K = J + p(s - 1)q^{s-2}.$$

The conditional variances and covariances are $k_{xx} = \Sigma m u_x^2$, etc.

In multiplex families the probability of r affected is $m_r = \binom{s}{r}p^r q^{s-r}\{1 - (1 - \pi)^r\}/\{1 - (1 - p\pi)^s - \pi spq^{s-1}\}$, with scores $u_p = r/pq - e_p$, $u_\pi = r(1 - \pi)^{r-1}/\{1 - (1 - \pi)^r\} - e_\pi$, where $e_p = s(D + q\pi K)/qD$ and $e_\pi = spJ/D$.

$$k_{pp} = s(s - 1)\{1 - (1 - \pi)^2(1 - p\pi)^{s-2}\}/q^2D + e_p/pq - e_p^2$$

$$k_{\pi\pi} = \sum_{r=2}^{s} m_r u_\pi^2$$

$$k_{\pi p} = s(s - 1)p(1 - \pi)(1 - p\pi)^{s-2}/qD + e_\pi/pq - e_p e_\pi$$

Among r affected, the distribution of a probands ($a > 0$) is $\binom{r}{a}\pi^a(1 - \pi)^{r-a}/\{1 - (1 - \pi)^r\}$, which corresponds to truncate selection of probands among affected sibs.

6. *Multiple selection* ($0 < \pi \leq 1$) *with at least one affected girl*

If a rare recessive trait is a mixture of autosomal and sex-linked cases, families with autosomal or sporadic cases will be recognized if they contain at least one affected girl. When $x = 0$, the distribution of r affected under this condition is

$$\binom{s}{r}p^r q^{s-r}\{1-(1-\pi)^r\}\{1-(1/2)^r\}/$$
$$\{1-(1-p\pi)^s-(p/2+q)^s+(p/2+q-p\pi/2)^s\}.$$

If x is the frequency of sporadic cases among affected girls, the frequency of simplex families is $m_1 = C(\pi/2)\{w+(1-w)spq^{s-1}/(1-q^s)\}$, and the frequency of multiplex families is

$$m_2 = C(1-w)\{1-(1-p\pi)^s-(p/2+q)^s+$$
$$(p/2+q-p\pi/2)^s-\pi spq^{s-1}/2\}/(1-q^s),$$

where

$$C = 1/\{w\pi/2+(1-w)\,[1-(1-p\pi)^s-$$
$$(p/2+q)^s+(p/2+q-p\pi/2)^s]/\,(1-q^s)\}.$$

Substituting for w,

$$m_1 = \frac{sp\pi\{x+(1-x)q^{s-1}\}}{xsp\pi+2(1-x)\{1-(1-p\pi)^s-(p/2+q)^s+(p/2+q-p\pi/2)^s\}} = sp\pi A/B,$$

say, and the scores for simplex families are

$$u_x = (BW-AY)/AB, \qquad u_\pi = (B-sp\pi Z)/\pi B,$$

and $u_p = (BX-spAV)/pAB$, where

$$V = x\pi+2(1-x)$$
$$\{\pi(1-p\pi)^{s-1}+(p/2+q)^{s-1}/2-(1+\pi)(p/2+q-p\pi/2)^{s-1}/2\}$$

$$W = 1-q^{s-1}$$

$$X = x+(1-x)q^{s-1}-p(1-x)(s-1)q^{s-2}$$

$$Y = sp\pi-2\{1-(1-p\pi)^s-(p/2+q)^s+(p/2+q-p\pi/2)^s\}$$

$$Z = x+2(1-x)\{(1-p\pi)^{s-1}-(p/2+q-p\pi/2)^{s-1}/2\}.$$

Similarly,

$$m_2 = \frac{2(1-x)\{1-(1-p\pi)^s-(p/2+q)^s+(p/2+q-p\pi/2)^s-\pi spq^{s-1}/2\}}{xsp\pi+2(1-x)\{1-(1-p\pi)^s-(p/2+q)^s+(p/2+q-p\pi/2)^s\}}$$
$$= 2(1-x)D/B,$$

say, and the scores for multiplex families are $u_x = -\{(1-x)Y+B\}/(1-x)B$, $u_\pi = sp(BJ-DZ)/BD$, and $u_p = s(BK-DV)/BD$, where

$$J = (1-p\pi)^{s-1}-(p/2+q-p\pi/2)^{s-1}/2-q^{s-1}/2$$

$$K = \pi(1-p\pi)^{s-1}+(p/2+q)^{s-1}/2-(1+\pi)(p/2+q-p\pi/2)^{s-1}/2-\pi q^{s-1}/2$$
$$+(s-1)\pi pq^{s-2}/2$$

The conditional variances and covariances are $k_{xx} = \Sigma u_x^2$, etc.

In multiplex families the probability of r affected is

$$m_r = \binom{s}{r} p^r q^{s-r}\{1 - (1 - \pi)^r\}\{1 - (1/2)^r\}/D,$$

with scores $u_p = r/pq - e_p$,

$$u_\pi = r(1 - \pi)^{r-1}/\{1 - (1 - \pi)^r\} - e_\pi,$$

where $e_p = s(D + qK)/qD$ and $e_\pi = spJ/D$.

$$k_{pp} = s(s - 1)\{1 - (1 - \pi)^2(1 - p\pi)^{s-2} - (p/2 + q)^{s-2}/4 + (1 - \pi)^2(p/2 + q - p\pi/2)^{s-2}/4\}/q^2D + e_p/pq - e_p^2$$

$$k_{\pi\pi} = \Sigma m_r u_\pi^2$$

$$k_{\pi p} = s(s - 1)p(1 - \pi)\left\{(1 - p\pi)^{s-2} - \left(\frac{p}{2} + q - \frac{p\pi}{2}\right)^{s-2}\Big/4\right\}\Big/qD + e_\pi/pq - e_\pi^2$$

As in §5, the distribution of a probands ($a > 0$) among r affected corresponds to truncate selection of probands among affected sibs.

If sex-linked and autosomal cases can be distinguished phenotypically, the distribution of r in families of the autosomal phenotype with no affected girl is the same as in §5, letting $p_0 = 1/7$ and defining x as the frequency of sporadic cases among affected boys. With girls excluded, $p_0 = 1/4$ on the same conditions.

7. *Estimation of π from the number of ascertainments*

Sometimes an investigator reports the number of times a family is ascertained instead of the number of probands. This extracts information from isolated cases, but requires for an estimate of π the assumption that ascertainments are independent.

Let there be t ascertainments of a family with r affected ($r > 0$), and let m be the mean number of ascertainments per affected individual, so that $\pi = 1 - e^{-m}$. The distribution of $t > 0$ is

$$P(t) = \frac{(mr)^t e^{-mr}}{t!(1 - e^{-mr})} = \frac{[-r \ln (1 - \pi)]^t (1 - \pi)^r}{t![1 - (1 - \pi)^r]}.$$

Then

$$u_\pi = -t/(1 - \pi) \ln (1 - \pi) - e_\pi$$

$$e_\pi = r/(1 - \pi)\{1 - (1 - \pi)^r\}$$

$$k_{\pi\pi} = \frac{r\{[1 - r \ln (1 - \pi)](1 - \pi)^r - 1\}}{(1 - \pi)^2[1 - (1 - \pi)^r]^2 \ln (1 - \pi)}.$$

The expected number of probands in a family with r affected is

$$a^* = r\pi/[1 - (1 - \pi)^r] = \pi(1 - \pi)e_\pi$$

When the probands are not designated, this method is open to objection because of uncertainty of the assumption that ascertainments are independent. Human

geneticists have not hitherto realized that the best analysis is possible only if the probands are designated, and in addition, *the number of ascertainments of each proband is recorded* and analysed by the method of this section for the case r = 1. These two estimates of π provide a test of the assumption that ascertainments are independent; this granted, the pooled estimate is more precise than probands or ascertainments alone could give.

It has been assumed above that ascertainment is sufficient to bring an individual into the record. This will not be true if some ascertained cases refuse to release their records or cooperate in other essential ways. However, the method is easily modified to adjust for this. Let there be N persons with at least one ascertainment, of whom n cooperate in the study. We agree to consider as a proband only patients who cooperate. Then if π' is the unadjusted ascertainment probability based on the distribution of t, and π the adjusted value,

$$\pi = n\pi'/N$$

$$K_{\pi\pi} = 1 \Big/ \left\{ \frac{n^2}{N^2 K_{\pi'\pi'}} + \frac{(N - n)\pi^2}{Nn} \right\}.$$

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The Inheritance of the Antigen Di^a: Evidence for Its Independence of Other Blood Group Systems

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FIG. 2 (*Continued*)

THE RED CELL ANTIGEN Di^a is not found, except as an extreme rarity, in the blood of Europeans or of West Africans: it is found in the blood of South American Indians, Japanese and Chinese and it is generally presumed to be a Mongolian character. Although the blood of some thousands of people of many races has been tested for anthropological purposes only five genetic studies of the antigen have been reported.

Layrisse, Arends and Dominguez Sisco, in 1955, gave pedigrees showing the inheritance of the antigen in four families, two from Caracas and two from Carib Indians. Layrisse and Arends (1957a) published a pedigree of the large Venezuelan family in which the antigen was first found. Other blood group antigens of this family were reported by Levine and Robinson (1957).

Lewis, Kaita and Chown (1957) gave one large Japanese pedigree in which Di^a was segregating: it included the details of the other groups. The authors also summarized the results of testing 50 Japanese families with anti-Di^a; the antigen was present in nine of the families.

Allen, in 1958, gave details of all the groups of 11 Peruvian Indian families possessing the antigen Di^a.

The present paper contributes nine Venezuelan families with the antigen Di^a which have been grouped for the other systems. Four of the families (Figure 1) are from Fajardo and five (Figure 2) are from Curiepe.

Fajardo is a modern village situated in the vicinity of Porlamar, Margarita Island. It has a hybrid population formed by intermixture of Guayquerí Indians, Whites (mainly Spaniards), and Negroes from West Africa. In a recent study (Layrisse, Wilbert and Arends, 1958) of blood group antigens in 103 unrelated natives of this village, it was shown that they have racial hybrid components of approximately 40 per cent Indian, 45 per cent Spanish and 12 per cent Negro. Although the Di^a antigen was found in 13 individuals, only four families were available for blood group studies.

The village of Curiepe has a Negro population of about 4,000 souls; it is situated on the Eastern coast of Miranda State. According to history, these Negroes have been in close contact with Carib Indians since Colonial times. The study of blood groups of 150 unrelated people from this population showed a frequency of 7 per cent Di(a+) (Layrisse, Arends and Dominguez Sisco, 1955; Layrisse and Arends,

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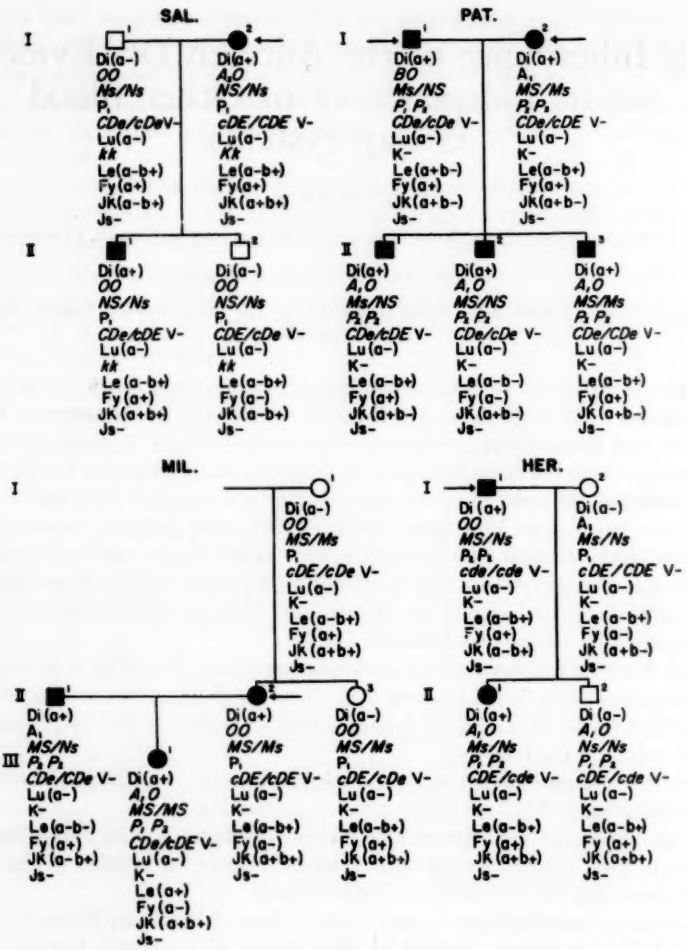

FIG. 1. Four Negro-Indian families from Margarita Island.

A blood group has been written in italics as a genotype wherever this is disclosed by the serological tests or by the combined evidence of serological tests and groups of other members of the family.

Antisera used as a routine: anti-Di^a; anti-A, -A_1, -B, -A + B; anti-M, -N, -S, -s; anti-P_1; anti-D, -C, -c, -C^w, -E, -e (only on E samples), -V; anti-Lu^a; anti-K; anti-Le^a, -Le^b; anti-Fy^a; anti-Jk^a, -Jk^b. The samples were tested with more than one example of most of the antisera.

Other antisera used: all members of the four families were negative with anti-Mi^a, anti-Vw and anti-Js. Families Sal. and Her. were tested with anti-f: Sal. I-1 and II-2 and Her. I-1, II-1 and II-2 were positive, the other members were negative. In Family Sal. all members were positive with anti-k and negative with anti-Kp^a. Pat. II-1, -2, -3 and Mil. III-1 were all positive with anti-Vel and anti-I.

1957b). Since the first blood group testing, carried out three years before the present study, some Di(a+) people have migrated to other places, making it possible to test only five families.

Three main questions to be asked in studying the inheritance of a new antigen

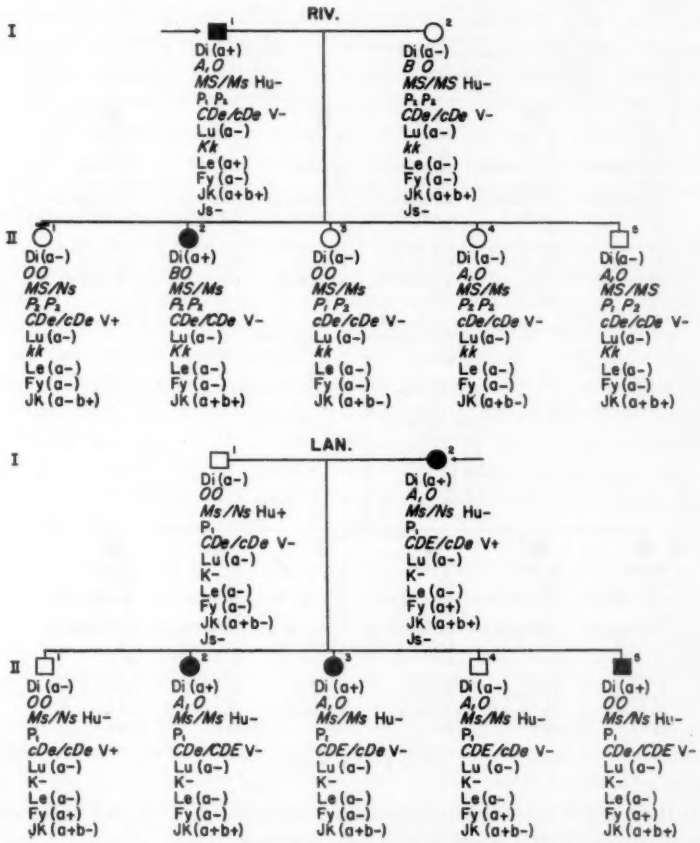

FIG. 2. Five Negro-Indian families from Curiepe.

Antisera used as a routine—see legend to Fig. 1.

Other antisera used: the 10 parents were tested with anti-Hu and anti-Js; children were tested only if a parent was positive. The parents were negative with anti-He, -Mi[a], -Vw, -M[g], -Vr, anti-P[k], anti-Kp[a] and anti-Levay. All members of the five families were Vel+ and all were I+ save the two group B people who were not tested. All members of Family Riv. were positive with anti-k. Family Lan. was tested with anti-f; only II-2 and II-5 were negative.

Two children are shown to be extramarital: Riv. II-1 by the MNSs and Rh groups and Mon. II-1 by the Rh groups.

In Family Lan., II-2, -3 and -4 show that the father's Hu+ gene must be travelling on his *Ns* chromosome: therefore II-1 and -5 have received their *Ns* from their mother. In Family Quin., II-2 and -6 show that the Hu+ gene is on the mother's *Ms* chromosome: it follows that the father has given *MS* to II-1 and *Ms* to II-2, -3, -4, -5, and -6.

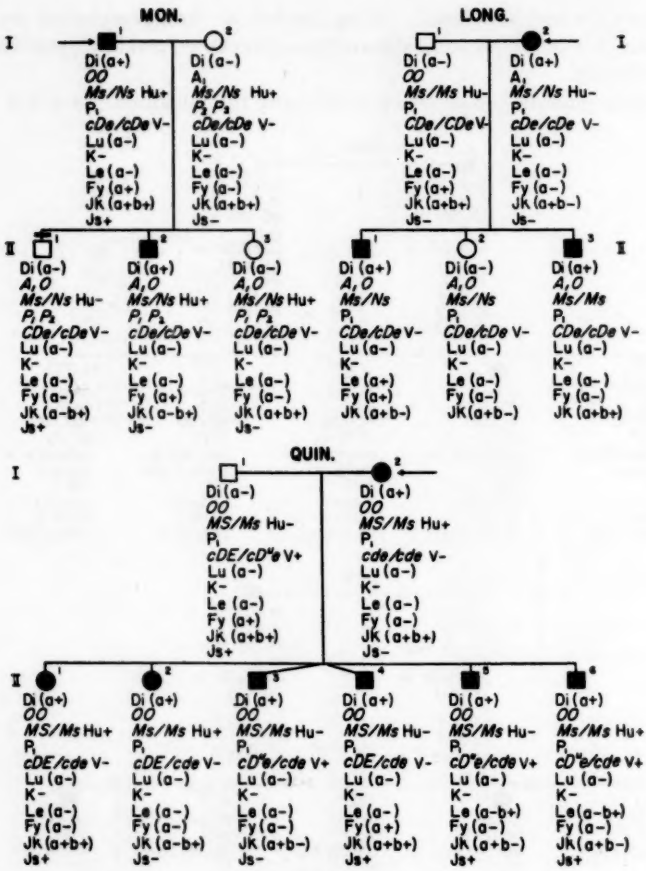

FIG. 2 (*Continued*)

are: 1. Is the antigen inherited as a dominant character? 2. Is it part of an already established system? 3. If it is not part of an established system, then is the new gene linked, in the classical sense of the word, to the genes for any of the established systems? As will be seen below, the first question can be answered, the second can now be almost completely answered and the third can be answered in part.

1. THE DOMINANCE OF THE ANTIGEN Di^a

The four families published by Layrisse, Arends and Dominguez Sisco (1955) made it appear very likely that the antigen was inherited as a dominant character, so did the family published by Layrisse and Arends (1957a). But the final proof had to await the paper of Lewis, Kaita and Chown (1957) which showed that a Di(a+) x Di(a+) mating could have Di(a−) children and, furthermore, that all of 111 children from 41 Di(a−) x Di(a−) matings were Di(a−).

2. THE INDEPENDENCE OF THE ANTIGEN Di^a OF OTHER ESTABLISHED SYSTEMS

This phase of the work is now nearly finished. As will be seen below, Diego has been proved independent of the ABO, MNSs, P, Rh, Kell, Duffy and Kidd systems. The independence can only be shown by testing families who have the Di^a antigen for the antigens of the other systems. The argument is based on the fact that recombination, which is the outward sign of crossing-over, has never been observed in the Rh or MNSs systems; it probably could happen but must be an extremely rare event. If therefore the genes for the Diego system segregate independently of the genes for, say, the ABO system we can be sure that the Di^a antigen is not a previously unknown part of that system. The only qualification is that illegitimacy could give a false appearance of independent segregation when the independence in segregation is the contribution of the sperm rather than of the ovum.

Families of two or more children are needed to show independent segregation of two genes and they have to be of certain mating types. The most informative kind of mating is that known as the double back-cross: in this type one parent must be heterozygous for both the genes being investigated and the destination, in the children, of this parent's genes must be clear. Family Lan. (Figure 2) serves as an example. The mother, I-2, is of the genotype *Di^{a}Di* for she has some *DiDi* children; she is also heterozygous A_1O for she has some *OO* children. Her contribution to the five children has been *Di*, *O*; *Di^a*, A_1; *Di^a*, A_1; *Di*, A_1 and *Di^a*, *O* respectively. The following is a simple way of seeing whether the children demonstrate that the two systems are not part of each other. The four possible contributions of the doubly heterozygous parent are written down thus:

Di^a	*Di*	*Di*	*Di^a*
A_1	*O*	A_1	*O*
2	1	1	1

The example gives what we may call an independence count of 3:2. If, as in this example, there be entries on both sides of the vertical line then the two gene systems being tested are proved not to belong to one and the same system. If all the entries be on one side of the vertical line it is probably a chance finding, but if it were a constant finding in other families then it would show that the two systems were one and the same. If in most families the entries were all on one side but in occasional families entries on both sides were found this would mean that the two systems were not part of each other but that their genes were linked in the classical sense; this type of linkage presents quite a separate problem and will be discussed in section 3 below.

In Table 1 are shown the independence counts for the nine families reported in this paper and those extracted from the published results of Levine and Robinson (1957), Lewis *et al.* (1957) and Allen (1958). It will be seen that the Di^a antigen does not belong to the ABO, MNSs, P, Rh, Kell, Duffy or Kidd systems; Di^a is also independent of the XY sex difference and it is not part of the system represented by the new negro antigen, Js, of Giblett (1958). Thus Diego is practically established as a new blood group system.

TABLE 1. INDEPENDENCE AND LINKAGE COUNTS FOR DIEGO AND OTHER SYSTEMS

		ABO	MNSs	P	Rh	Lu^a	Kell	Duffy	Kidd	Js	Sec.	Le^a in saliva	Partial sex
Levine and Robinson, 1957			4:2		4:3				2:1				2:2
					3:1								
Lewis, Kaita and Chown, 1957		3:2	2:0	2:1									1:1
		1:1	1:1										3:2
			1:1										2:0
Allen, 1958	V. 6			1:1									1:1
	V. 9		2:0		3:2								
	V. 10												2:0
	V. 11	2:1	3:0	2:1	2:1								
	V. 13												4:2
	V. 18		1:1		2:0								
	V. 28												2:1
	V. 36				2:2								4:0
Margarita Island	Sal.	1:1	1:1		2:0		1:1		2:0				
	Pat.												
	Mil.												1:1
	Her.		1:1										2:0
Curiepe	Riv.	3:1	2:2	3:1	4:0		3:1		2:0				2:2
	Lan.	3:2	3:2		4:1			4:1	4:1				
	Mon.							2:0		1:1			2:0
	Quin.												
	Long.		2:1										

For completeness, mention should be made of another way in which a new antigen may be shown to belong to, or at least be influenced by, an old system. If the frequency of the new antigen is not the same in each of the different divisions of a known system then the antigen probably belongs to that system. For example, the observation that the antigen S was more common in samples of blood of group M than of group N gave the first indication that S was part of the MN system. A more extreme example is the antigen Tj^a which was recognized as belonging to the P system when all Tj(a−) persons tested at that time were found to be negative with anti-P_1. The method can only show dependence, it cannot prove independence. Allen (1958) applied this method to samples from 308 Peruvian Indians tested for Di^a and for ABO, MNS, P, Rh, Lewis and Duffy without any association disclosing itself.

3. LINKAGE RELATIONS OF THE DIEGO GENES

The genes for the Diego system having been proved independent of all the established systems, save Lutheran, secretor, and the Lewis saliva groups, the independence counts given in Table 1 become the counts needed to search for linkage, in the ordinary sense of the word, between the locus for Diego and the loci for the other blood group systems.

TABLE 2. THE LINKAGE SCORES, λ, AND THE INFORMATION, κ, FOR THE FAMILIES LISTED IN TABLE 1

	$\Sigma(\lambda)$	$\Sigma(\kappa)$	$1.64\sqrt{\Sigma(\kappa)}$
ABO	−7.219	30.978	9.13
MNSs	−6.000	43.550	10.82
P	−3.766	11.669	5.60
Rh	+2.000	64.000	13.12
Kell	−1.000	7.000	4.34
Duffy	+2.879	11.082	5.46
Kidd	+3.000	15.000	6.35
Js	−1.111	0.988	1.63
Partial sex	−1.000	53.000	11.94

No data are yet available for Lutheran, secretion or for the presence of the Le^a antigen in the saliva.

In the analysis the *u* statistics of Fisher (1935) have been used as elaborated by Finney (1940). Only "certain" families have been scored and they have been treated as the following "mating types" of Finney: ABO one 18, rest 13; MNSs two 17, one 18, rest 16; P one 14, rest 13; Rh two 17, rest 16; Kell 16; Duffy 13; Kidd two 16, two 17; Js 13; partial sex 16. The results are given in Table 2. The last column shows the significance of the results. Finney states that if $\Sigma(\lambda)$ exceeds $1.64\sqrt{\Sigma(\kappa)}$ then linkage is established at the 1 in 20 level of probability. It will be seen that there is no evidence of linkage in any of the comparisons though the information in some is too small to exclude loose linkage. We can say that the Diego locus if it be on the same chromosome as any of the following loci is not within measurable distance of them: ABO, MNSs, P and Rh; nor if the Diego locus be on the homologous part of the sex chromosomes is it in measurable distance of the beginning of the non-homologous region.

The independence of Di^a of "private" and "public" antigens

The antigen Di^a having been excluded from belonging to all the established blood group systems, save Lutheran, secretion and the Lewis saliva groups, it remains to exclude it as far as possible from belonging to the less well worked out "private" and "public" groups.

Certain "private" and "public" antigens that on further investigation have been found to belong to the established systems are of course excluded when the system to which they belong is shown to be independent of Di^a. Thus Hu, He, Mi^a, Vw (Gr), Vr, M^g and S^u all belong to the MNSs system and therefore must be independent of Di^a—so also must Tj^a which belongs to the P system and Kp^a and Kp^b which belong to the Kell system.

Since it is extremely unlikely that the antigen Di^a will be found segregating in a family which is also segregating for a rare antigen, such as Wr^a, or for a very common antigen, such as Yt^a, no independence counts will be possible and the independence of Di^a of such antigens has to be investigated in other, less certain, ways.

Exclusion of "private" antigens. Several examples of Di(a+) red cells have been tested and found negative with antisera to the following "private" antigens: Levay, Wr^a, Rm, Be^a and By and several unpublished examples. Conversely, anti-Di^a has

given negative reactions with samples of red cells which are Levay+, Wr(a+) or Be(a+). This proves that Di^a is not the same antigen as, for example, Wr^a and we know that Di^a is not the same as Wr^b, for all Wr(a−) white people so far tested have been Di(a−). On the other hand, we have no evidence to refute a possible suggestion that Di^a is the product of a hypothetical third allele Wr^c (or $Levay^c$ or Rm^c or Be^c or By^c).

Exclusion of "public" antigens. Anti-Vel and anti-I are clearly not anti-Di^a: neither are they the theoretical anti-Di^b for both antibodies have reacted positively with samples which should include a homozygote Di^aDi^a. (The cells were from Quin. I-2, Figure 2, who has six children Di(a+) and from Pat., II-1, -2 and -3 and Mil. III-1, Figure 1, each of whom has at least a 25 per cent chance of being Di^aDi^a.) Furthermore, the red cells of one Vel negative and one I negative person have been found to be Di(a−). Similarly anti-Yt^a is not anti-Di^b for the cells of one Yt(a−) person have been tested with anti-Di^a and found to be negative.

If it be true that Quin. I-2 is homozygous Di^aDi^a then neither of the two known anti-Di^a sera demonstrated a dosage effect, for these cells reacted no more strongly than did those of people known to be heterozygous Di^aDi.

Independence of Di^a and Js

By extraordinary good fortune the Mongolian antigen Di^a and the Negro antigen Js (Giblett, 1958) were both present in the red cells of the father, I-1, in family Mon. (Figure 2) and, what is more, the two antigens segregate independently: the father has given Di^a to his son II-2 without Js and he has given Di to his daughter II-3 also without Js. Only in people of mixed Negro-Mongolian stock could this independence have been established.

The family Quin. (Figure 2) gives some valuable new information about the independence of Js. In Giblett's original paper Js is reported to have segregated independently of ABO, MNSs and Rh. The family Quin. shows Js segregating independently of MNSs (3:3), Rh (3:3), Duffy (3:3) and Kidd (3:1). It also shows that Js is independent of sex (4:2).

Ten separate loci are known to be involved in controlling the antigens of the red cells and saliva—ABO, secretor, MNSs, P, Rh, Lutheran, Kell, Le^a in saliva, Duffy and Kidd; the antigens Di^a and Js almost certainly define two more.

SUMMARY

Previous work has shown that the antigen Di^a is inherited as a dominant character. Inspection of the published pedigrees shows that the antigen does not belong to the systems ABO, MNSs, P, Rh or Kidd. The families here reported confirm these observations and add Kell, Duffy and Js to the systems excluded. Only Lutheran, secretion and the Lewis saliva groups remain to be excluded for Diego to achieve the status of a new blood group system.

Evidence is produced that if the Diego locus be on the same chromosome as any of the following loci it is not within measurable distance of them: ABO, MNSs, P or Rh; If the Diego locus be on the homologous part of the sex chromosomes it is not within measurable distance of the beginning of the non-homologous region.

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ADDENDUM

Since the writing of this paper Chown, Lewis and Kaita (1958, Nature 181: 1598–9) have reported the results of testing their Japanese family, given in Table 1, with anti-Fy^b. *Di*^{a} segregated independently of *Fy*^{b}.

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A "New" Antigen and Antibody Belonging to the P Blood Group System

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FROM THE TIME OF THEIR DISCOVERY, by Landsteiner and Levine in 1927, the P groups remained apparently simple and innocuous until 1955 when Sanger recognized that the antigen Tj^a of Levine, Bobbitt, Waller and Kuhmichel (1951) belonged to the P system.

The P system shows remarkable parallels to the A_1A_2O system which are useful at least as an aid to remembering the details of P. Tables 1 and 2 are reproduced in the hope that they will serve as a summary of knowledge of the system at the beginning of the present investigation.

The genetic relationship of A_1 to A_2 is clear—they represent alleles, but the serological relationship of A_1 to A_2 is obscure and little serological illumination is contributed to the P system by the analogy. The notation for the antigens and antibodies concerned with A_1 and A_2 is not entirely happy but, since it is the best that anyone has been able to think of in nearly half a century, we feel we ought to apply it to the P system. It is generally believed that A_1 has two antigens, A_1 and A, while A_2 has only one, A. Anti-A sera contain two antibodies, anti-A and anti-A_1. It is unfortunate that anti-A is used with two meanings—both for the serum and for one of the antibodies in the serum. However, it is usually clear from the context in which sense the term anti-A is being used.

So we think of P_1 as having two antigens, P_1 and P, and P_2 as having only one, P. This is how we think of the antibodies: 1) anti-P corresponds to anti-A in its restricted sense and it reacts with P_1 and P_2 cells by virtue of their common antigen P; 2) anti-P+P_1 corresponds to anti-A in its broad sense and is a mixture of anti-P and anti-P_1; 3) anti-P_1 corresponds to anti-A_1 and reacts only with P_1 cells; 4) when referring in general terms to the antibodies belonging to the P system we propose to call them P antibodies or P antisera.

The gene p is extremely rare: only nine unrelated pp people have been reported and all of them were selected in that the anti-P+P_1 in their serum called them to notice: more than 10,000 random people have been tested with anti-P+P_1 without a single negative having been found. The importance of the phenotype p lies in the revolution it has made in our way of thinking of the P system.

THE PRESENT INVESTIGATION

A sample of blood from Mrs. Mys. was sent in 1956 to the War Memorial Blood Bank for pre-operative grouping and cross-matching. The serum agglutinated or sometimes lysed the cells of all of 150 prospective donors tried, but it did not react

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TABLE 1. THE EXPANDED P SYSTEM (after Sanger, 1955)

ANTIBODIES	anti-P_1	(previously called anti-P)
	anti-P + P_1	(previously called anti-Tj^a)
ANTIGENS	P_1	(previously called P)
	P_2	(previously called p) — previously called Tj^a
	p	(previously called Tj^b)

Phenotypes Anti − P + P_1	Phenotypes Anti − P_1	Genotypes	Approximate European Frequencies
+	+	P_1P_1	29%
		P_1P_2	50%
		P_1p	0%
+	−	P_2P_2	21%
		P_2p	0%
−	−	pp	0%

TABLE 2. THE P SYSTEM AND THE A_1A_2O MODEL (after Sanger, 1955)

Presence of antigens and antibodies

Red Cell Phenotype	Antibodies in Serum	Red Cell Phenotype	Antibodies in Serum
O	always anti-A + A_1	p	always anti-P + P_1
A_2	sometimes anti-A_1	P_2	sometimes anti-P_1
A_1	none	P_1	none

Behaviour of antigens and antibodies

Anti-A + A_1	Anti-P + P_1
Absorption by A_2 cells leaves anti-A_1. Eluate from absorbing cells reacts more strongly with A_1 than with A_2 cells.	Absorption by P_2 cells leaves anti-P_1. Eluate from absorbing cells reacts more strongly with P_1 than with P_2 cells.
Absorption by A_1 cells removes all antibody. Anti-A_1 is the last component to be removed.	Absorption by P_1 cells removes all antibody. Anti-P_1 is the last component to be removed.

with the patient's own cells. As a result the operation, a minor one, was cancelled. Mrs. Mys. has had five children and one miscarriage; she has never been transfused.

The serum was reinvestigated in 1957: it was tested against thawed samples of cells lacking "public" antigens: "Bombay", Vel negative, S^uS^u, Fy(a−b −), Yt(a−) and I negative cells were agglutinated but p cells were not. The strength of the positive reactions was increased by the addition of Löw's papain solution. These were the results of testing the serum against 11 samples of thawed red cells, the three p samples being from unrelated persons:

		Cells p	Cells P_1 and P_2	
Mys. serum	+	0	8	probability = 1 in 165
	−	3	0	

So the problem appeared to be solved; we assumed that Mrs. Mys. was of the genotype *pp* and that her antibody was the anti-P+P_1 normally present in the serum of such people. It seemed that all that remained to do was to get a sample of red cells from Mrs. Mys. and show that they were negative with anti-P+P_1 and with anti-P_1 sera. The problem was, in fact, just beginning, for when the sample arrived

the cells were agglutinated by all the five anti-P+P_1 and the eight best anti-P_1 sera in our collection.

It was difficult to believe that the red cells of Mrs. Mys. could really be P_1 when her serum contained an antibody against P_1 and P_2 cells. It seemed more reasonable to attribute the positive reaction of her cells with anti-P+P_1 and with anti-P_1 to some extra antibody present in these sera. The results of absorption tests show that an extra antibody was indeed responsible. When anti-P+P_1 sera were absorbed with the cells of Mrs. Mys. they lost their power to agglutinate her cells but still reacted strongly with P_1 and P_2 cells. Similarly, anti-P_1 sera after absorption with the cells of Mrs. Mys. still agglutinated P_1 cells. The presence of the extra antibody was confirmed when anti-P+P_1 absorbed by P_1 cells (until it no longer reacted with P_1 cells) was found still to react with the cells of Mrs. Mys. The extra antibody present in the anti-P+P_1 and in the anti-P_1 sera we are calling anti-P^k. The results of the absorption tests are summarized in Table 3.

Further tests on the serum of Mrs. Mys. showed that it contains anti-P and not, as we assumed at first, anti-P+P_1. Absorption with P_2 cells failed to leave anti-P_1

TABLE 3. ANALYSIS, BY ABSORPTION, OF THE ANTIBODIES IN CERTAIN SELECTED P ANTISERA

Antisera	Red Cells				Review of Antibody Content
	P_1	P_2	p	P^k (Mys.)	
1. anti-P_1	+	−	−	+	anti-P_1 + P^k
2. anti-P + P_1	+	+	−	+	anti-P + P_1 + P^k
3. Mys. serum	+	+	−	−	anti-P
4. Mys. serum abs. × P_2 cells	−	−	−	−	
5. anti-P_1 abs. × Mys. cells	+	−	−	−	anti-P_1
6. anti-P + P_1 abs. × Mys. cells	+	+	−	−	anti-P + P_1
7. anti-P + P_1 abs. × P_1 cells	−	−	−	+	anti-P^k
8. anti-P + P_1 abs. × P_2 cells	+	−	−	+	anti-P_1 + P^k

TABLE 4. THE EFFECT OF ABSORBING TWO EXAMPLES OF ANTI-P + P_1 + P^k SERA

An Easily Spittable Serum

Cells	Anti-P + P_1 + P^k (El.)						
	Unabs.	Absorbed by P_1 Cells			Absorbed by P^k Cells (Mys.)		
		Once	Twice	Thrice	Once	Twice	Thrice
P_1	37	+++	(+)	0	30	28	25
P_2	+++	0	0	0	+++	+++	+++
p	0	•	•	•	•	•	•
P^k (Mys.)	36	30	30	30	2	0	0

A Serum Showing Some Cross-reaction

Cells	Anti-P + P_1 + P^k (Pa.)						
	Unabs.	Absorbed by P_1 Cells			Absorbed by P^k Cells (Mys.)		
		Once	Twice	Thrice	Once	Twice	Thrice
P_1	33	0	0	0	21	15	11
P_2	+++	0	0	0	n.t.	+++	++
p	0	•	•	•	•	•	•
P^k (Mys.)	31	13	8	3	0	0	0

The figures are scores given to titrations in saline; the symbols +++ etc. are the reactions with undiluted serum when the serum has not been titrated; n.t. = not tested.

TABLE 5. SUMMARY OF INHIBITIONS OF ANTI-P_1 AND ANTI-P^k BY HYDATID CYST FLUID

		Antisera		
		Anti-P_1 + P^k	Anti-P + P_1 + P^k	Anti-P (Mys.)
component antibodies	anti-P	•	weak inhibition	no inhibition
	anti-P_1	strong inhibition	strong inhibition*	•
	anti-P^k	strong inhibition	strong inhibition	•

* Most clearly shown by absorbing anti-P + P_1 + P^k with P_2 cells: this leaves anti-P_1 + P^k which is strongly inhibited by the hydatid cyst fluid.

TABLE 6. DETAILS OF THE INHIBITIONS, BY HYDATID CYST FLUID, SUMMARIZED IN TABLE 5

Anti-P_1 + P^k

Cells	Kauf.		App.		Sher.	
	sal.	h.c.	sal.	h.c.	sal.	h.c.
P^k (Mys.)	16	0	12	0	2	0
P_1	53	0	43	0	28	0
P_2	0		0		0	

Anti-P

Cells	Mys.		her sister, II-8	
	sal.	h.c.	sal.	h.c.
P^k (Mys.)	0		0	
P_1	33	28	32	36
P_2	21	19	26	32

Anti-P + P_1 + P^k

Cells	El.		Pa.		Herr K.		Brom.	
	sal.	h.c.	sal.	h.c.	sal.	h.c.	sal.	h.c.
P^k (Mys.)	37	0	28	0	43	0	17	0
P_1	30	18	32	8	43	25	24	11
P_2	30	18	19	8	36	21	20	5

The sera were titrated and 1 volume of saline (sal.) or hydatid cyst fluid (h.c.) was added to each tube: 1 volume of Löw's papain solution was added to all tubes in the titrations of Mys., II-8 and Herr K. sera. The figures are scores given to the resulting agglutination.

(Table 3) and the absence of anti-P_1 was supported by the failure of hydatid cyst fluid to inhibit the reaction of the serum with P_1 cells (see below).

Table 3 also shows that six different types of P antisera exist, or can be made by absorption: the useful diagnostic sera are anti-P (or anti-P+P_1, which gives the same reactions), anti-P_1 and anti-P^k.

Not all examples of P antisera can be split as neatly as those shown in Table 3: in some there is interference by cross reaction. Details of absorptions of two anti-P+P_1+P^k sera are given in Table 4.

Though absorption, even if repeated, of anti-P_1+P^k sera by P^k cells leaves a pure anti-P_1, absorption by P_1 cells removes both antibodies; two anti-P_1+P^k sera were tried. Effective absorption in one direction only has been described in certain group O sera [Harley (1936), Dodd (1952), and Bird (1953)]. However, a pure anti-P^k can be made by absorbing anti-P+P_1+P^k serum by P_1 cells.

No example of anti-P^k was found when the sera of 69 normal people were tested against saline suspensions of the cells of Mrs. Mys. It will be seen from the footnote to Table 7 that none of the "private" antibodies there listed is anti-P^k.

The fluid from hydatid cysts of sheep's livers inhibited anti-P_1 and partly inhibited anti-$P+P_1$, but it did not inhibit other antibodies tested (Cameron and Staveley, 1957, Staveley and Cameron, 1958). The fluid also inhibits anti-P^k. The inhibitions are summarized in Table 5 and some detailed examples are given in Table 6. It will be seen from Tables 5 and 6 that hydatid fluid causes some inhibition of the anti-P in anti-$P+P_1+P^k$ sera but no inhibition of the anti-P in anti-P sera (Mys. and II-8). Evidently anti-P is not inhibited by hydatid fluid: the appearance of some inhibition of anti-P in anti-$P+P_1+P^k$ sera could be understood if we allow that some of the antibody molecules in such sera are mixed ones. If molecules exist which are anti-PP_1 or anti-PP^k we would expect them to be inhibited by the hydatid fluid. Heterologous inhibition by A or B substance of the anti-B or anti-A in certain group O sera has been described [Dodd (1952) and Bird (1953)].

Why anti-P is not inhibited by hydatid cyst fluid, when anti-P_1 and anti-P^k are inhibited, clearly presents a problem.

THE INHERITANCE OF P^k

The blood groups of all available members of the family of Mrs. Mys. are given in Table 7. The results with the three diagnostic P antisera, anti-P, anti-P_1 and anti-P^k, are also shown in the pedigree in Figure 1.

The antigen P^k has been found in the red cells of only one other member of the family, II-8, a sister of Mrs. Mys. In the serum of this sister anti-P is also present.

If the antigen P^k be inherited as a straighforward dominant character it must have come from the father, I-1, who is dead, for the mother, I-2, lacks it. Half the children of I-1 would be expected to have P^k and so would half the children of II-4 and II-8. From the count we should exclude the proposita, and we are left with 13 children, 6.5 of whom we expect to have P^k but only one does have it. Applying Yates' correction, χ^2 for 1 d.f. = 7.7 for which the probability is less than 1 in 150.

It is therefore practically certain that the antigen is not inherited as a straightforward uncomplicated dominant character and we have to consider what ways of inheritance will fit the observed results.

1). In the pedigree P^k looks like a recessive character: one of the four sibs of the proposita has the antigen, which is just what would be expected. However, we are very suspicious of this easy solution, for now that the Le^a antigen of the red cells is no longer considered a recessive character there is no example in man, or, as far as we know, in any other species, of a red cell antigen that appears only when the corresponding allele is present in double dose. (Even if a weak anti-O or anti-H reagent alone were available the antigens O and H would not fit the definition of a recessive character for they appear when the gene *O* is present in single dose in the genotype A_2O.) If I-1 and I-2 were cousins we would have to accept the antigen as a recessive character, but they are not related as far as is known, and though they both come from Finland they come from different parts of the country.

2). Another possibility, rather easier to accept, is that one gene P^k can cause the antigen but only in the absence of the genes P_1 and P_2 higher in the series. That is to say the antigen appears only when the genotype is P^kp or P^kP^k.

3). A further possibility that has to be considered is that two different genes at

TABLE 7. THE BLOOD GROUPS OF THE FAMILY OF MRS. MYS. (II-4)

Pedigree No.	P antisera						ABO	MNSs	Rh	Lu^a	K	Le^aLe^b		Fy^a
	1	2	3	4	5	6								
I-2	+	+	+	+	+	−	A_1B	*MS/MS*	*CDe/cDE*	−	−	−		+
II-1	+	+	+	+	+	−	A_1	*MN·Ss*	*cDE/cde*	−	−	−		+
II-2	+	+	+	+	+	−	A_1	*MN·Ss*	*cDE/cde*	−	−	+		+
II-3	+	+	+	+	+	−	O	*Ns/Ns*	*CDe/cde*	−	−	−	+	+
II-4	+	+	−	−	−	+	B	*MS/MS*	*cDE/cde*	−	−	−		−
III-1	+	+	+	+	+	−	O	*MS/Ns*	*CDe/cDE*	−	−	−	+	−
III-2	+	+	+	+	+	−	B	*MS/Ns*	*CDe/cDE*	−	−	−		−
III-3	+	−	+	+	−	−	O	*MS/Ns*	*CDe/cDE*	−	−	−	+	+
III-4	+	+	+	+	+	−	O	*MS/Ns*	*cDE/cde*	−	−	−	+	+
III-5	+	−	+	+	−	−	B	*MS/Ns*	*CDe/cDE*	−	−	−	+	+
II-5	+	+	+	+	+	−	A_1	*MS/NS*	*cDE/cde*	−	−	−		+
II-6	+	+	+	+	+	−	B	*MS/MS*	*cDE/cDE*	−	−	−	+	+
II-7	+	−	+	+	−	−	O	*Ms/Ms*	*cde/cde*	−	−	−	+	+
II-8	+	+	−	−	−	+	B	*MS/NS*	*cDE/cDE*	−	−	−		+
III-6	+	−	+	+	−	−	B	*Ms/NS*	*cDE/cde*	−	−			+
III-7	+	−	+	+	−	−	O	*MS/Ms*	*cDE/cde*	−	−			+
II-9	+	+	+	+	+	−	B	*MS/MS*	*CDe/cde*	−	−	−		+

P antisera used:

1 = anti-P + P_1 + P^k (five examples)
2 = anti-P_1 + P^k (three or more examples)
3 = anti-P + P_1 (anti-P + P_1 + P^k abs. × P^k cells)
4 = anti-P (serum of Mys., II-4, and of her sister, II-8)
5 = anti-P_1 (anti-P_1 + P^k abs. × P^k cells)
6 = anti-P^k (anti-P + P_1 + P^k abs. × P_1 cells)

Other antisera used:

anti-A, -B, -A + B; anti-M, -N, -S, -s; anti-C, -c, -C^w, -D, -E, -e; anti-Lu^a; anti-K; anti-Le^a, -Le^b, anti-Fy^a. The cells of II-4, Mrs. Mys., were negative with the following antisera: anti-Hu, -He, -Mi^a, -Vw, -Vr, -M^g, -C^x, -E^w, -V, -Kp^a, -Wr^a, -Di^a, -By, -Rm, and -Be^a; they were positive with anti-H, -Ss, -Kp^b, -Vel and -I. Saliva of II-4, -6 and -8 was tested and found to contain B, H and Le^a. Anti-P_1 was detectable in the serum of III-3, -5 and -6.

the *P* locus interact to produce the antigen P^k. This has to be remembered for such an interaction has been described in the rabbit by Cohen (1956 and 1958). An allelic series, Hg^A, Hg^D and Hg^F, exists; each allele makes its own red cell antigen, A, D or F as the case may be; but the heterozygote Hg^A/Hg^D, besides making A and D, makes a new antigen, I, not made by any other genotype. Were the background not known I would be assumed to be a recessive antigen.

4). Yet another possibility is that the antigen P^k is the product of the interaction of the gene P^k with a gene at another locus: alternatively such a gene might have to be absent before P^k can express itself. Invoking interaction with a separate locus

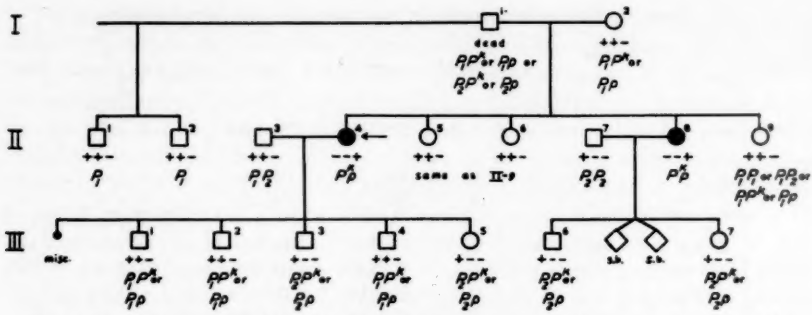

FIG. 1. The P phenotypes of the family Mys. together with a possible genotypic interpretation. Black = antigen P^k present; hollow = P^k absent; arrow = proposita.

The plus and minus signs represent the reactions of the samples with the three antisera anti-P, anti-P_1 and anti-P^k, in that order.

might seem unnecessarily far fetched an explanation were it not the background of the human red cell antigen Le^a. (Le^a appears on the cells when the gene *L* is present at the Lewis locus and when the gene *Se* is absent from the unlinked secretor locus.)

5). An inhibitor gene seems to be excluded: it could explain the absence of the antigens P and P_1 from the cells of II-4 and II-8 but it could hardly explain the presence of the antigen P^k.

There is little to choose between the first four possibilities, though we are prejudiced against 1, the hypothesis of an uncomplicated recessive antigen. As an example of how genotypes can be fitted to the family reactions we have, in the pedigree, used the second hypothesis and supposed that Mrs. Mys. is of the genotype P^kp. We have written P^kp rather than P^kP^k because it seems that the gene p is more frequent than P^k. We think p must be more frequent than P^k because the red cells of three unrelated people who possess the anti-Tj^a type of antibody were available for testing with anti-P^k and all of them were negative, that is to say they are all pp. Furthermore the sera of two other unrelated people of this sort have been tested and found to contain anti-$P+P_1+P^k$ showing that they also come from pp and not from P^k donors.

Table 8 shows the four P phenotypes defined by the three separate antibodies now available. The genotypic interpretation is based on hypothesis 2. (If hypothesis 1 were correct the only change would be that the genotype P^kp would have to be moved down to join pp in the bottom category.)

The final decision about the precise genetic background will have to await the testing of more families. Perhaps the incidence of the antigen in these families or the evidence of cousin matings will give the clue. If we had to find the families by testing random donors with anti-P^k the quest would be hopeless, for the antigen P^k may have a frequency of the order of one in a million. But this is not how more families will be found: attention will be drawn to them as to the Mys. family, by trouble arising from the presence of the antibody. The huge net of the transfusion services will inevitably catch more examples of such a rarity, but they will have to be waited for.

TABLE 8. THE FOUR P PHENOTYPES WHICH HAVE BEEN OBSERVED AND THEIR GENOTYPIC INTERPRETATION

Phenotypes Anti			Genotypes
-P	-P_1	-P^k	
+	+	−	P_1P_1 P_1P_2 P_1P^k P_1p
+	−	−	P_2P_2 P_2P^k P_2p
−	−	+	P^kP^k P^kp
−	−	−	pp

Whatever its precise genetic background, and however infrequent the antigen may be, P^k has disclosed the existence of a common antibody, anti-P^k, and it gives a glimpse of the complexity of a system which only three years ago appeared to consist of one antigen and one antibody.

SUMMARY

The study of an antibody which had been the cause of cross-matching difficulties has led to the recognition of P^k, a new and very rare antigen belonging to the P system. The antigen was found in the red cells of two sisters both of whom have anti-P in their serum. Antisera previously thought to be anti-P+P_1 and anti-P_1 have been shown to contain a further antibody, anti-P^k.

A fourth allele at the *P* locus is required to explain P^k. It is probable that the gene P^k can only express itself in the genotype P^kp or P^kP^k, that is to say, when P_1 and P_2 are absent.

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Study on the Genetics of Human Eye-brows

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ROZPRYM (1934) PUBLISHED a classic work on eye-brows and eye-lashes, based on 524 individuals in the small town of Lissen near Brno. Later, Basu (1941) examined 200 cases among the Bengalis in Calcutta. The hereditary influence was not examined by Basu. Rozprym only casually mentioned the genetic aspect of the problem.

In 1957, I had an opportunity to examine the eye-brow types and whorl-patterns of 83 families in Delhi. The examination covered 501 individuals of different age-groups, and both sexes. No surviving member of a family was left out of the survey so that as complete a picture of the genetic pattern as possible, could be obtained. The families were drawn from the main segments of the Delhi population e.g. the Bengalis, the Tamils, the Telugus, the Sindhis, the Punjabis, and Uttar Pradesh Banias and Kayasthas, though the Bengalis were by far the largest group examined. The Bengali families have been classified separately into (1) Brahmins, (2) Baidyas, (3) Kayasthsa and (4) Others. The first three being distinct, generally endogamous, caste-units while the fourth is a heterogeneous group which includes castes other than the first three. Similarly, the Uttar Pradesh families have been separately classified into the two castes, the Kayasthas and the Banias. No Uttar Pradesh Brahman family was represented in the sample. Table 1 shows the familial distribution of eye-brow and whorl types.

I used the method of examination and system of nomenclature of the eye-brow types and whorls, introduced by Rozprym (1934). Since the symbols used by Rozprym (e.g. a for spreading, b for Even etc) were not easily identifiable with the types they were intended to represent, they have been abandoned for a separate notation such as Sp for the spreading type, E for the Even type of eye-brow etc.

Two eye-brow forms mentioned by Rozprym, namely, (1) the "shedding" type and (2) the "S-shaped" type, call for a little explanation:

(1)"Shedding" type: This does not appear to constitute a distinct type by itself Among the cases studied by Rozprym, this trait was found only among 1 per cent of the sample. They were all over 45 years and, according to Rozprym, most of the hairs in their eyebrows had fallen out, (possibly the reason for the nomenclature). I had five cases which could fall under this category (Table 2A). They were in the age-range 41–50 years and above. Four of these (family 8 Bengali Brahmin, 2 Bengali Baidya, 6 and 7 Bengali Kayastha, Table 1), which were re-checked by me, showed by the contour and the hair-stream of their eye brows, unmistakable resemblance to N, Sp, A and Sp types respectively. The "shedding" type may not, therefore, be a basic type.

(2) "S-shaped". Only one case of this type was found (family 5. Bengali Brahmin, Table 1). Rozprym, too, found only one case of S-type while Basu found none among

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TABLE 1. DISTRIBUTION BY FAMILIES OF EYEBROW AND WHORL-PATTERN[1, 2]

No.	Parents		Children	Total No.	
	Male	Female		Male	Female
BENGALI BRAHMINS					
1	PC′(62)	× SpN′(58)	F SpC′(14), M PC′(20), M SpC′(17), M SpC′(35) (× F SpC′(27), F SpC′(11), M SpC′(7)), F SpC′(33) (× M-M SpE′(11), F SpC′(9), M (SpE′(7), F SpC′(2)), F SpE′(38) (X M-F PN′(23), M SpE′(22), F PN′(15), F SpC′(11)), F NC′(36) (X M SpC′-(40) M SpE′(16), F SpC′(15), F NC′(5)), F NC′(28) (X M PN′-(38) F NC′(7), M EN′(5), F NC′(3))	12	17
2	SpC′(60)	× SpC′(48)	M NE′(28), FNE′(22) (X M SpC′-(27) M SpC′(½), × F NC′(½)) F NC′(19), F NC′(17), F NC′(14), F SpC′(12), M SpC′(8)	5	7
3	PC′(61)	× SpC′(49)	M PC′(30) (X F NE′(21), F NE′(1)), M PE′(20), F PC′(18), M PC′(16)	4	4
4	—	× SpC′(55)	M SpC′(32) (× F SpC′-(24) F SpC′(9), F SpC′(7), M SpE′(6))	2	4
5	SpC′(60)	× SE′(50)	M SpN′(31) (× F NC′(20) − F NN′(2), M SpN′(½)), M SpC′(25), F NC′(22), M SpC′(20), F PC′(17), M PC′(14), M PC′(11)	7	5

[1] Figures with parentheses indicate the respective age of the individuals.

[2] The following abbreviations have been used for the eye-brow types and the whorl-patterns:

1. Eye Brow Types

(i)	Spreading	Sp
(ii)	Arched	A
(iii)	Falling	F
(iv)	Rising	R
(v)	S-Shaped	S
(vi)	Shedding	Sh
(vii)	Peaked	P
(viii)	Narrowing	N
(ix)	Even	E

2. Whorl-Patterns

(i)	Concentric	C′
(ii)	Eccentric	E′

In addition, N′ indicates the absence of a whorl, and stands for Neutral.

M and F prefixed to a pheno-type stands for a male and a female respectively e.g. F SpC′ is a female with Spreading brow-type and Concentric whorl.

TABLE 1.—*Continued*

No.	Parents		Children	Total No.	
	Male	Female		Male	Female
6	SpC′(40)	× SpC′(22)	M SpC′(15), M SpC′(12), M SpC′(9), F SpC′(6)	4	2
7	PC′(41)	× EC′(34)	M EC′(14), M EC′(10)	3	1
8	ShN′(48)	× SpE′(38)	M SpE′(13), F SpE′(7)	2	2
9	SpC′(33)	× SpE′(23)	M SpN′(½)	2	1
10	SpN′(44)	× NC′(36)	M SpN′(12), F NN′(2½)	2	2
11	AC′(53)	× EC′(42)	F EC′(23), M AC′(20)	2	2
12	SpC′(60)	× EC′(50)	F PC′(24), F PC′(20), M SpC′(19), F PC′(15), F SpC′(14), F PC′(10)	2	6
13	SpN′(52)	× FC′(40)	M SpN′(15), F FN′(13), M SpC′(10), M SpE′(8), M FN′(5), F SpC′(3)	5	3
14	FE′(49)	× SpC′(37)	M SpE′(13), M FE′(11)	3	1
15	PE′(54)	× AC′(43)	F PC′(18), F AC′(16), M AC′(14), M PN′(13), M PE′(6)	4	3
16	SPN′(51)	× SpC′(38)	F SpC′(14), M SpC′(12), F SpC′(7)	2	3
17	SpC′(37)	× SpC′(26)	F SpN′(5), F SpC′(4)	1	3
18	SpN′(58)	× PC′(48)	M SpN′(21), F SpN′(18)	2	2
19	PN′(32)	× NC′(27)	M PC′(6), M PN′(2)	3	1
Total				67	69
BENGALI BAIDYAS					
1	SpN′(53)	× NE′(44)	F PC′(24), M NC′(20), M SpE′(12), M NE′(9)	4	2
2	SpC′(57)	× ShC′(47)	M NC′(31) (× F NC′(27)- M NC′(7), M NC′(6)), F EC′(15), F EC′(13)	4	4
3	AC(55)	× NC′(44)	F AC′(24), F NE′(22), F AC′(20)	1	4
4	SpC′(48)	× SpE′(34)	F SpE′(14), M SpC′(12)	2	2
5	AN′(43)	× EC′(31)	M EC′(12), F EC′(6)	2	2

TABLE 1.—*Continued*

No.	Parents		Children	Total No.	
	Male	Female		Male	Female
6	—	× ShC′(54)	F FN′(35) (× M FN′(51)- M EE′(6)), M FC′(21)	3	2
7	PC′(45)	× PN′(36)	M PN′(11), M PC′(9), F PC′(5)	3	2
8	PN′(65)	× PC′(50)	F PC′(28), F PC′(22)	1	3
9	PN′(38)	× SpC′(25)	F SpN′(11), F SpN′(4), F SpN′(2)	1	4
Total				21	25
BENGALI KAYASTHAS					
1	SpC′(64)	× SpC′(56)	M SpC′(36) (× F SpC′(28)- M SpC′(9), M SpC′(6)), F SpE′(30)	4	3
2	—	× NC′(50)	M NC′(36) (× F NC′(30)- M NN′(6), M NN′(3)), M NC′(34), F NC′(16)	4	3
3	SpC′(60)	× SpC′(50)	F SpC′(22), M PN′(20), F SpC′(19)	2	3
4	PC′(56)	× EC′(38)	F EC′(14), M PN′(10)	2	2
5	SpN′(58)	× NC′(48)	F NC′(26) (× M SpN′(37)- F NC′(3))	2	3
6	ShN′(52)	× NE′(39)	F NC′(21), F AE′(16), F NC′(13), M AC′(7), F NE′(3)	2	5
7	—	× ShC′(74)	M SpC′(56) (× F NN′(39)- F PC′(19), M PC′(17), M SpE′(10), M PC′(6), F PC′(1))	4	4
8	FN′(41)	× SpN′(34)	F SpC′(11), M AC′(6), M SpN′(3)	3	2
9	NN′(34)	× SpC′(27)	F SpN′(7), F SpC (5), F NC′(4)	1	4
10	PC′(39)	× SpC′(25)	F PC′(7), F PC′(3)	1	3
Total				25	32
BENGALI (OTHERS)					
1	—	× SpC′(66)	M SpC′(52) (× F PC′(41)- F PC′(25), F SpC′(21), M SpC′(19), F PC′(12) M PC′(9), M SpC′(1)	4	5
2	PC′(30)	× PC′(21)	M PC′(5), F PC′(3), F PC′(1½)	2	3
3	SpE′(43)	× SpC′(33)	F SpC′(18), M PC′(17), M PE′(12), F SpE′(8)	3	3

TABLE 1.—*Continued*

No.	Parents		Children	Total No.	
	Male	Female		Male	Female
4	SpC′(30)	× EC′(23)	F NN′(6), F EC′(4), F EC′(2)	1	4
5	PN′(55)	× SpC′(35)	F SpC′(14), M SpC′(12), M SpC′(10)	3	2
6	PN′(48)	× FN′(35)	M RC′(18), M RC′(13), M PC′(12), M FC′(3)	5	1
7	PC′(41)	× SpN′(31)	F SpN′(9), F SpC′(6), M SpC′(4), M SpC′(2)	3	3
8	SpN′(50)	× —	M SpN′(25)- (× F PE′(30),- F PN′(12), F PN(9), F SpN′(5), F SpC′(3), F SpN(1½)	2	6
Total				23	27
PUNJABIS					
1	SpC′(55)	× EC′(50)	M EC′(34) (× F EC′(24)- F EC′(3½)), M SpC′(30) (× F EC′(26)- M EC′(3)), F EC′(19), M EC′(14)	5	5
2	SpC′(57)	× SpC′(48)	M NN′(33) (× F EC(29)- F NE′(9), M NC(7), F NC(5), M NC(2)) M SpC′(28), F SpC′(14)	5	5
3	PN′(38)	× AE′(36)	F PC′(8), F PE′(5½), M PE′(4½)	2	3
4	NC′(42)	× PC′(33)	M EE′(14), F NC′(11), M NE′(9), F NC′(3½)	3	3
5	AC′(36)	× SpC′(34)	M AC′(15), M AN′(5)	3	1
6	SpN′(36)	× PN′(31)	M PC′(5), M PC′(3), M PC′(2)	4	1
7	PE′(39)	× SpN′(37)	F PN′(16), F PC′(13), F PC′(10), F PC′(6), F PC′(2½)	1	6
8	SpN′(39)	× NC′(32)	M PN′(12), F SpC′(5)	2	2
9	RC′(34)	× NC′(27)	M NC′(10), M NN′(8), M AC′(7)	4	1
10	AN′(29)	× RC′(26)	F RN′(2), F RN′(½)	1	3
11	SpN′(26)	× SpN′(24)	M SpN′(3), M SpN′(1)	3	1
12	PC′(39)	× NC′(30)	F PC′(7), M PC′(1)	2	2
13	PN′(59)	× SpC′(46)	M PC′(25), M PC′(23), F SpC′(19)	3	2

TAALE 1. (*Continued*)

No.	Parents		Children	Total No.	
	Male	Female		Male	Female
14	PC′(41)	× EC′(40)	F PC′(19), M PC′(17), M EC′(15), F PC′(10), F PC′(5), M PN′(1)	4	4
15	PC′(44)	× NN′(38)	F PC′(13), M NN′(11), M NC′(9), M NC′(7), F NC′(5)	4	3
16	PN′(47)	× NC′(36)	M PN′(16), F NC′(15), M PC′(8), M NC′(7)	4	2
17	PC′(58)	× PN′(48)	M PN′(21), M PN′(18), F PC′(17), F PC′(13)	3	3
18	PC′(40)	× SpN′(30)	F PC′(11), M NN′(10), F PC′(6), M PC′(2), M PN′(1)	4	3
19	PN′(56)	× PC′(51)	F PC′(15), F PC′(12), M PC′(10), M PC′(8)	3	3
20	PC′(42)	× SpC′(35)	F PC′(17), F NC′(15), M SpC′(12), M PC′(10), M NC′(8)	4	3
21	SpN′(32)	× RN′(21)	F SpN′(4), M SpN′(2)	2	2
Total				66	58
TELUGU (ANDHRA)					
1	SpC′(47)	× PC′(37)	F SpC′(9), M PC′(7), M SpN′(5)	3	2
Total				3	2
TAMIL (MADRAS)					
1	NE′(41)	× SpE′(31)	M SpC′(12), F SpC′(10), M SpE′(9), M NE′(8), F NC′(6), F SpC′(4)	4	4
2	AC′(32)	× SpC′(32)	M AC′(3), M SpC′(½)	3	1
Total				7	5
SINDHI					
1	SpN′(46)	× PC′(32)	F SpC′(19), M PC′(15), F SpC′(9), M SpC′(4)	3	3
Total				3	3
BANIAS (UTTAR PRADESH)					
1	PN′(33)	× PC′(30)	F PN′(9), F PN′(5)	1	3
2	FN′(47)	× PN′(40)	F PN′(22), M PN′(18), M FN′(14), F PN′(12), F RC′(10), F PN′(7)	3	5

TABLE 1.—*Concluded*

No.	Parents		Children	Total	
	Male	Female		Male	Female
3	NC′(26)	× FN′(22)	F NC′(3)	1	2
4	FN′(32)	× SpN′(25)	M SpC′(7), M SpN′(4), F SpN′(2)	3	2
5	AN′(52)	× NC′(45)	M EC′(23), M PC′(21), M EC′(20), M AC′(19), F NE′(13), M NC′(11)	6	2
Total				14	14
KAYASTHAS (UTTAR PRADESH)					
1	AC′(40)	× SpN′(35)	F SpE′(13), F SpC′(7)	1	3
2	RC′(37)	× SpN′(30)	M SpN′(8), M SpN′(5)	3	1
3	NC′(42)	× PN′(35)	F EN′(11), M PN′(9), F NN′(5)	2	3
4	FN′(47)	× PN′(41)	F PN′(14), F PN′(12), M PN′(10), F PN′(7), F PN′(6), M PE′(2)	3	5
5	PC′(34)	× SpC′(28)	F SpC′(10), M SpC′(8), M PN′(6)	3	2
6	PN′(31)	× SpC′(27)	M SpC′(9), M SpN′(2)	3	1
7	PC′(54)	× AN′(50)	F NN′(19), F PN′(18), M PC′(17), M PC′(15), M AC′(13)	4	3
Total				19	18
Grand total				248	253

TABLE 2. A—DISTRIBUTION OF EYEBROW TYPES BY AGE-GROUPS

Age	Brow Types																		Total
	SP		P		N		E		A		F		R		Sh		S		
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
A. MALES																			
0–10	34	39.6	25	29.1	16	18.6	4	4.6	5	5.8	2	2.3	x	x	x	x	x	x	86
11–20	18	31.6	21	36.8	3	5.2	6	10.4	5	8.8	2	3.6	2	3.6	x	x	x	x	57
21–30	8	44.4	5	27.7	2	11.1	1	5.6	1	5.6	1	5.6	x	x	x	x	x	x	18
31–40	11	32.4	11	32.4	5	14.7	1	2.9	3	8.9	1	2.9	2	5.8	x	x	x	x	34
41–50	7	29.2	8	33.3	3	12.5	x	x	1	4.2	4	16.6	x	x	1	4.2	x	x	24
Over 50	14	48.4	10	34.5	x	x	x	x	3	10.3	1	3.4	x	x	1	3.4	x	x	29
Total	92	37.1	80	32.2	29	11.7	12	4.8	18	7.2	11	4.4	4	1.7	2	0.9	x	x	248
B. FEMALES																			
0–10	29	39.2	22	29.7	18	24.3	2	2.7	x	x	x	x	3	4.1	x	x	x	x	74
11–20	18	28.1	24	37.5	11	17.2	7	10.9	3	4.7	1	1.6	x	x	x	x	x	x	64
21–30	16	34.8	9	19.6	12	26.1	5	10.9	1	2.2	1	2.2	2	4.2	x	x	x	x	46
31–40	18	45.0	7	17.5	7	17.5	3	7.5	2	5.0	3	7.5	x	x	x	x	x	x	40
41–50	5	22.7	5	22.7	5	22.7	4	18.4	1	4.5	x	x	x	x	1	4.5	1	4.5	22
Over 50	4	57.2	1	14.3	x	x	x	x	x	x	x	x	x	x	2	28.5	x	x	7
Total	90	35.5	68	26.9	53	20.9	21	8.3	7	2.9	5	1.9	5	1.9	3	1.3	1	0.4	253

TABLE 2. B—DISTRIBUTION OF WHORL PATTERNS BY AGE

Age	Whorl-Patterns						Total
	C′		E′		N′		
	No.	%	No.	%	No.	%	
A. MALES							
0–10	48	55.8	13	15.1	25	29.1	86
11–20	38	66.6	8	14.2	11	19.2	57
21–30	11	61.1	2	11.1	5	27.8	18
31–40	19	55.9	1	2.9	14	41.2	34
41–50	11	45.8	3	12.5	10	41.7	24
Over 50	16	55.2	1	3.4	12	41.4	29
Total	143	57.6	28	11.3	77	31.1	248
B. FEMALES							
0–10	49	66.2	5	6.7	20	27.1	74
11–20	45	70.3	5	7.8	14	21.9	64
21–30	33	71.7	6	13.1	7	15.2	46
31–40	22	55.0	6	15.0	12	30.0	40
41–50	17	77.2	2	9.2	3	13.6	22
Over 50	6	85.7	x	x	1	14.3	7
Total	172	68.0	24	9.5	57	22.5	253

his subjects. It is not clear whether the S-shaped trait is a distinct type. Among the seven children of family 5 (Bengali Brahmin, Table 1), there were none who inherited the trait.

Rozprym mentioned, besides the two main types of whorls, two exceptional types, the Concrescent and the Approaching, where the glabella is overgrown with hairs. Such exceptional forms did not come to my notice among the subjects examined. The difference in these cases from the principal types of whorls may not be more than one of degree rather than of kind. Several cases were found, corresponding to case 33 of Rozprym, where the concentric whorl was not fully penetrant, and it had developed only on one side of the glabella. Such cases have been marked with an asterisk in Table 1. Variability in expression was a feature among whorls, that could be easily noticed.

Table 2A-B and Table 3 are supplementary to Table 1. Table 2 gives the distribution of brow-types and whorls by age-groups. Table 3 shows the frequency distribution of eye-brow forms and whorl-patterns, separately for each group of the population, and also, the extent of association of a whorl-type with an eye-brow type. Frequencies differ from group to group, and between the sexes. The chi-square difference between the frequencies of brow-types among males and that among females, is 18.82 (df = 8, P between .02 and .01). The corresponding difference for whorls is 5.91 (df = 2, P = .05).

Biswas (1956) measured the degree of association of several pairs of atrributes e.g. the hair colour and the eye-colour, the skin colour and the eye colour of the Santals by means of Karl Pearson's Co-efficient of Mean square Contingency (Udny Yule *et al*, 1940). The co-efficient was calculated for several pairs of whorls and brow-types. They are:

Combination	Males	Females
Spreading-Concentric	.0192(.9 > P > .8)	.0214(.9 > P > .8)
Peaked-Concentric	.0104(P = .90)	.0174(.9 > P > .8)
Narrowing-Concentric	.0024(P = .98)	.0379(P = .70)
Spreading-Eccentric	.0614(.7 > P > .5)	.035(P = .70)

df = 1

Taking P = .05 as the limit of significance, the deviation from chance expectation was, in none of these cases, significant.

The phenotypes of the parents and the off-spring (Table 4) suggest a genetic influence on the inheritance-pattern of eye-brows. The precise mechanism is, however, not clear. Spreading eye-brow may reasonably be assumed to be the dominant form, since no child has the spreading type of eye-brow without having at least one parent with the trait. An attempt was made to interpret the data on the basis of a multiple allelic series in the order, $A \rightarrow a^0 \rightarrow a^1 \rightarrow a^2 \rightarrow a^3 \rightarrow a^4 \rightarrow a^5 \rightarrow a^6$ (for Sp, S, A, F, P, N, E, and R type respectively). Difficulties however, arose in allocating the several observed types in the allelic series. The status of S-type which appears in one parent and no children, is indeterminate. Further, there are 7A children to 21 non-A children from crosses between Arched and types other than Arched.

Spreading, a result somewhat unexpected from the dominant-recessive relationship assumed. The proportion of F children to non-F children (2 F:16 non-F) arising from crosses between F and types other than Sp and A, is equally disconcerting. Nor is it

TABLE 3. DISTRIBUTION OF WHORL-PATTERNS AMONGST THE DIFFERENT EYE-BROW TYPES

Whorl-patterns	Brow types																		Total (Whorls)
	Sp		P		N		E		A		F		R		Sh		S		
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
A. MALES																			
1. *Bengali Brahmins*																			
C′	22	61.1	9	25.0	x	x	2	5.5	3	8.4	x	x	x	x	x	x	x	x	36
E′	8	57.2	3	21.5	1	7.1	x	x	x	x	2	14.2	x	x	x	x	x	x	14
N′	10	58.8	4	23.5	x	x	1	5.9	x	x	1	5.9	x	x	1	5.9	x	x	17
Total (Eye-brows)	40	59.6	16	23.9	1	1.5	3	4.5	3	4.5	3	4.5	x	x	1	1.5	x	x	67
2. *Bengali Baidyas*																			
C′	3	25.0	2	16.6	4	33.2	1	8.4	1	8.4	1	8.4	x	x	x	x	x	x	12
E′	1	33.4	x	x	1	33.3	1	33.3	x	x	x	x	x	x	x	x	x	x	3
N′	1	16.7	3	49.9	x	x	x	x	1	16.7	1	16.7	x	x	x	x	x	x	6
Total (Eye-brows)	5	23.9	5	23.9	5	23.9	2	9.5	2	9.4	2	9.4	x	x	x	x	x	x	21
3. *Bengali Kayastha*																			
C′	6	42.9	4	28.5	2	14.3	x	x	2	14.3	x	x	x	x	x	x	x	x	14
E′	1	100.0	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	1
N′	3	30.0	2	20.0	3	30.0	x	x	x	x	1	10.0	x	x	1	10.0	x	x	10
Total (Eye-brows)	10	40.0	6	24.0	5	20.0	x	x	2	8.0	1	4.0	x	x	1	4.0	x	x	25
4. *Bengali, Others*																			
C′	8	47.0	6	35.3	x	x	x	x	x	x	1	5.9	2	11.8	x	x	x	x	17
E′	1	50.0	1	50.0	x	x	x	x	x	x	x	x	x	x	x	x	x	x	2
N′	2	50.0	2	50.0	x	x	x	x	x	x	x	x	x	x	x	x	x	x	4
Total (Eye-brows)	11	47.8	9	39.2	x	x	x	x	x	x	1	4.3	2	8.7	x	x	x	x	23
5. *Telugu (Andhra)*																			
C′	1	50.0	1	50.0	x	x	x	x	x	x	x	x	x	x	x	x	x	x	2
E′	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
N′	1	100.0	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	1
Total (Eye-brows)	2	66.7	1	33.3	x	x	x	x	x	x	x	x	x	x	x	x	x	x	3

6. *U. P. Kayasthas*																			
C′	2	20.0	4	40.0	1	10.0	x	x	2	20.0	x	x	1	10.0	x	x	x	x	10
E′	x	x	1	100.0	x	x	x	x	x	x	x	x	x	x	x	x	x	x	1
N′	3	37.5	4	50.0	x	x	x	x	x	x	1	12.5	x	x	x	x	x	x	8
Total (Eye-brows)	5	26.2	9	47.3	1	5.3	x	x	2	10.6	1	5.3	1	5.3	x	x	x	x	19
7. *U. P. Banias*																			
C′	1	14.3	1	14.3	2	28.5	2	28.6	1	14.3	x	x	x	x	x	x	x	x	7
E′	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
N′	1	14.3	2	28.6	x	x	x	x	1	14.3	3	42.8	x	x	x	x	x	x	7
Total (Eye-brows)	2	14.3	3	21.4	2	14.3	2	14.3	2	14.3	3	21.4	x	x	x	x	x	x	14
8. *Tamil (Madras)*																			
C′	2	50.0	x	x	x	x	x	x	2	50.0									4
E′	1	33.3	x	x	2	66.7													3
N′	x	x	x	x	x	x													x
Total (Eye-brows)	3	42.8	x	x	2	28.6	x	x	2	28.6									7
9. *Sindhi*																			
C′	1	50.0	1	50.0															2
E′	x	x	x	x															x
N′	1	100.0																	1
Total (Eye-brows)	2	66.7	1	33.3															3
10. *Punjabis*																			
C′	5	12.9	18	46.2	8	20.6	4	10.2	3	7.6	x	x	1	2.5	x	x	x	x	39
E′	x	x	2	50.0	1	25.0	1	25.0	x	x	x	x	x	x	x	x	x	x	4
N′	7	30.4	10	43.5	4	17.4	x	x	2	8.7	x	x	x	x	x	x	x	x	23
Total (Eye-brows)	12	18.2	30	45.4	13	19.7	5	7.6	5	7.6	x	x	1	1.5	x	x	x	x	66
SUMMARY																			
C′	51	35.6	46	32.2	17	11.9	9	6.3	14	9.8	2	1.4	4	2.8	x	x	x	x	143
E′	12	42.8	7	25.0	5	17.8	2	7.2	x	x	2	7.2							28
N′	29	37.7	27	35.1	7	9.1	1	1.3	4	5.2	7	9.1	x	x	2	2.5	x	x	77
Total (Eye-brows)	92	37.1	80	32.2	29	11.7	12	4.8	18	7.2	11	4.4	4	1.7	2	0.9	x	x	248

	Concentric		Eccentric		Neutral		Total No.
	No.	%	No.	%	No.	%	
Whorls	143	57.6	28	11.3	77	31.1	248

TABLE 3.—*Continued*

Whorl-patterns	Brow types																		Total (Whorls)
	Sp		P		N		E		A		F		R		Sh		S		
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
B. FEMALES																			
1. *Bengali Brahmins*																			
C′	25	47.2	8	15.1	13	24.5	4	7.6	2	3.8	1	1.8	x	x	x	x	x	x	53
E′	4	50.0	x	x	3	37.5	x	x	x	x	x	x	x	x	x	x	1	12.5	8
N′	3	37.5	2	25.0	2	25.0	x	x	x	x	1	12.5	x	x	x	x	x	x	8
Total (Eye-brows)	32	46.4	10	14.5	18	26.1	4	5.8	2	2.9	2	2.9	x	x	x	x	1	1.4	69
2. *Bengali Baidyas*																			
C′	1	6.2	5	31.3	2	12.5	4	25.0	2	12.5	x	x	x	x	2	12.5	x	x	16
E′	2	50.0	x	x	2	50.0	x	x	x	x	x	x	x	x	x	x	x	x	4
N′	3	60.0	1	20.0	x	x	x	x	x	x	1	20.0	x	x	x	x	x	x	5
Total (Eye-brows)	6	24.0	6	24.0	4	16.0	4	16.0	2	8.0	1	4.0	x	x	2	8.0	x	x	25
3. *Bengali Kayastha*																			
C′	9	36.0	4	16.0	9	36.0	2	8.0	x	x	x	x	x	x	1	4.0	x	x	25
E′	1	25.0	x	x	2	50.0	x	x	1	25.0	x	x	x	x	x	x	x	x	4
N′	2	66.6	x	x	1	33.4	x	x											3
Total (Eye-brows)	12	37.5	4	12.5	12	37.4	2	6.2	1	3.2	x	x	x	x	1	3.2	x	x	32
4. *Bengali, Others*																			
C′	8	47.0	6	35.3	x	x	3	17.7	x	x	x	x	x	x	x	x	x	x	17
E′	1	50.0	1	50.0	x	x	x	x	x	x	x	x	x	x	x	x	x	x	2
N′	4	50.0	2	25.0	1	12.5	x	x	x	x	1	12.5	x	x	x	x	x	x	8
Total (Eye-brows)	13	48.2	9	33.3	1	3.7	3	11.1	x	x	1	3.7	x	x	x	x	x	x	27
5. *Telugu (Andhra)*																			
C′	1	50.0	1	50.0	x	x													2
E′	x	x	x	x	x	x													x
N′	x	x	x	x	x	x													2
Total (Eye-brows)	1	50.0	1	50.0	x	x													2
6. *U. P. Kayasthas*																			

Total (Eye-brows)	1	50.0	1	50.0	x	x													2
6. U. P. Kayasthas																			
C′	4	100.0	x	x											x	x	x	x	4
E′	1	100.0	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	1
N′	2	15.4	7	53.8	2	15.4	1	7.7	1	7.7	x	x	x	x	x	x	x	x	13
Total (Eye-brows)	7	38.9	7	38.9	2	11.1	1	5.5	1	5.6	x	x							18
7. U. P. Banias																			
C′	x	x	1	25.0	2	50.0	x	x	x	x	x	x	1	25.0	x	x	x	x	4
E′	x	x	x	x	1	100.0	x	x	x	x	x	x							1
N′	2	22.2	6	66.7	x	x	x	x	x	x	1	11.1	x	x	x	x	x	x	9
Total (Eye-brows)	2	14.3	7	50.0	3	21.4	x	x	x	x	1	7.2	1	7.1	x	x	x	x	14
8. Tamil (Madras)																			
C′	3	75.0	x	x	1	25.0	x	x	x	x	x	x	x	x	x	x	x	x	4
E′	1	100.0	x	x	x	x	x	x											1
N′	x	x	x	x															x
Total (Eye-brows)	4	80.0	x	x	1	20.0	x	x											5
9. Sindhi																			
C′	2	66.7	1	33.3	x	x	x	x	x	x	x	x	x	x	x	x	x	x	3
E′	x	x	x	x	x	x													x
N′	x	x	x	x	x	x	x	x									x	x	x
Total (Eye-brows)	2	66.7	1	33.3	x	x													3
10. Punjabis																			
C′	7	15.9	19	43.2	10	22.7	7	15.9	x	x	x	x	1	2.3	x	x	x	x	44
E′	x	x	1	33.3	1	33.3	x	x	1	33.4	x	x							3
N′	4	36.3	3	27.3	1	9.1	x	x	x	x	x	x	3	27.3	x	x	x	x	11
Total (Eye-brows)	11	18.9	23	39.6	12	20.7	7	12.2	1	1.7	x	x	4	6.9	x	x	x	x	58
SUMMARY																			
C′	60	34.9	45	26.2	37	21.5	20	11.6	4	2.4	1	0.6	2	1.2	3	1.6	x	x	172
E′	10	41.7	2	8.3	9	37.5	x	x	2	8.3	x	x	x	x	x	x	1	4.2	24
N′	20	35.2	21	36.9	7	12.3	1	1.8	1	1.8	4	6.8	3	5.2	x	x	x	x	57
Total (Eye-brows)	90	35.5	68	26.9	53	20.9	21	8.3	7	2.9	5	1.9	5	1.9	3	1.3	1	0.4	253

	Concentric		Eccentric		Neutral		Total
	No.	%	No.	%	No,	%	
Whorls	172	68.0	24	9.5	57	22.5	253

TABLE 4. FREQUENCY OF PHENOTYPES OF CHILDREN FROM PARENTAL CROSSES

Phenotypes of Parents	No. of families	Brow-types								Family size
		Phenotypes of children								
		SP	S	A	F	P	N	E	R	
Sp × Sp	10	23	—	—	—	—	—	—	—	1, 2, 2, 2, 2, 2, 2, 3, 3, 4
	2	4	—	—	—	3	—	—	—	3, 4
	2	4					6	—	—	3, 7
Sp × S	1	3				3	1			7
Sp × A	1			2						2
	1	2								2
	1	1		1						2
Sp × F	2	5			3					2, 6
	1	3								3
	1	2		1						3
Sp × P	6	14				10	—	—	—	3, 3, 3, 4, 5, 6
	5	14								2, 2, 3, 3, 4
	2	6				3	4	—	—	5, 8
	4					14				2, 3, 4, 5
	1					4	1			5
Sp × N	6	11					7			2, 2, 2, 3, 3, 6
	1	1				1	2			4
	2	2				5				2, 5
	2						2			1, 1
Sp × E	1	1						3	—	4
	1							1		1
	1	2				4				6
	1						1	2		3
Sp × R	2	4								2, 2
Sp × Sh(?)	1	2								2
	1	x					1	2		3
Total	59	104	x	4	3	47	25	8	x	191
A × P	1	—	—	x		3				3
	1			2	—	3				5
	1			1		3	1			5
A × N	1			2			1		—	3
	1			1		1	2	2	—	6
A × E	1							2	—	2
	1			1				1		2
A × R	1								2	2
Total	8			7	x	10	4	5	2	28
F × F	1							1	—	1
F × P	2				2	5			3	4, 6
	1					6				6
F × N	1						1		—	1
Total	5				2	11	1	1	3	18
P × P	6					18			—	2, 2, 3, 3, 4, 4

TABLE 4.—*Continued*

Phenotypes of Parents	No. of families	Brow-types: Phenotypes of children								Family size
		SP	S	A	F	P	N	E	R	
P × N	2					4				2, 2
	2				—	3	6		—	4, 5
	1						1			1
	1					1	1	1	—	3
	2						5	2		3, 4
P × E	2					6	—	2	—	2, 6
	1							2	—	2
Total	17					32	13	7	—	52
N × N	2						4	—	—	2, 2
N × E	1						4			4
N × R	1			1			2			3
Total	4			1			10			11
E × E	1						—	1	—	1
Sh(?) × N	1			2			3			5
Total (a)	95	104	0	14	5	100	56	22	5	306

(a) Includes sub-families

TABLE 5. FREQUENCY OF PHENO-TYPES OF CHILDREN FROM PARENTAL CROSSES

Parents	Whorls																Pheno-types of children
	C′ only		E′ only	N′ only	C′ + E′ Total			C′ + N′ Total			E′ + N′ Total			C′ + E′ + N′ Total			
C′ × C′																	
1	2				1	5		3	10								C′ = 86
2	8			1	4	2	1	6		3							E′ = 9
3	2				1		3			6							N′ = 12
4	2						2										—
5	1				1			1									107
6	2									1							
7							1										
C′ × N′																	
1	3				1	5		3	9						1		C′ = 73
2	2		6				1	4	3	3				1			E′ = 6
3	3		2		1			4		3					x	1	N′ = 36
4	2				1		1	1		3							—
5					1		3			3						1	115
6							1										
7					1												
8							1										
N′ × E′																	
1					1			1	1								C′ = 11
2		1			1	3											E′ = 8
3					1		1										N′ = 5
4							1	1	1								—
5							1			2							24
N′ × N′																	
1		1						2	1		1						C′ = 11
2			2					1	1								E′ = 2
3	1									2							N′ = 17
4	1																—
5								1			1						30
6										1							
C′ × E′																	
1	x	1	1		1	1		x	1	x	—	—	—	—	1	1	C′ = 14
2	1	1			1	1	1										E′ = 7
3														1			N′ = 3
4							1										—
5																1	24
6								1									
7										1							
E′ × E′																	
2						1											C′ = 4
4					1												E′ = 2
6							1										N = 0
																	—
																	6
Total	82	6	25		50	25	(75)	62	39	(101)	1	5	(6)	5	2	4 (11)	306

possible, on this hypothesis, to account for the A child from the cross, N × R. The attempt was abandoned.

The mode of inheritance of whorls seems to be more complex. Not infrequently, are there E′ and N′ children, beside C′, from C′ × C′ crosses. Similarly there are C′ and E′ children, beside N′, from crosses between N′ and N′ parents (Table 5). The data however, point to a tendency among the children to resemble, phenotypically, their parents more than would be expected on a random basis.

Conclusion: The data for eye-brows and whorls show an inherited tendency among the children, though the mode of inheritance cannot be determined at this time.

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Handedness: A Family Study

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INVESTIGATIONS into the determination of hand preference have been directed either toward the biological or the environmental aspects of human personality development. Of potentially related phenomena, other functional asymmetries, speech, intelligence, vocational aptitude and some very specific behavior patterns have been subjected to scrutiny. Procedurally, hand preference has been measured by the questionnaire method, demonstration tests, or psychomotor tests.

Twins have received particular attention, since they are supposed to have a significantly higher frequency of left-handedness than do single-born individuals. There is disagreement on the type of zygosity group (one-egg or two-egg) showing an increased proportion of left-handers (Dahlberg, 1926; Rife, 1940; Husèn, 1955).

The theory of a cramped fetal position as the most plausible cause of this increase in twins has been questioned (Overstreet, 1938). With the fetus being in constant rotation throughout its development, neither the apparent prenatal position nor a certain kind of birth presentation can really be expected to be indicative of subsequent laterality. Moreover, left-handedness and twinning seem to be independent phenomena (Torgersen, 1950).

Four major family studies on hand dominance have been conducted in the last 50 years, all of them by means of questionnaires. The probands were university students who provided information on their own hand preference and by correspondence on the hand preference of their parents and siblings. In this manner, the distribution of right- and left-handedness in the offspring was determined in relation to the handedness of the parents. The genetic mechanism controlling hand preference was classified as simple recessive by Ramaley (1913), as undetermined by Chamberlain (1928) and as a graded quantitative (polygenic) trait by Rife (1940). In Trankell's (1955) statistical reevaluation of these first three studies, attention was called to the agreement in the data obtained by these investigators. Merrell (1957) doubted that the genesis of handedness can be accounted for independently by either hereditary or environmental factors.

The main objectives of the present study of hand preference variations in families of New York City school children were (a) to determine the cause or causes and total expressivity range of hand preference and (b) to establish, if possible, a family pattern of hand dominance which would explain the distribution of right- and left-handedness in children of all four types of parental combination.

The following questionnaire, based partly on the work of Hull (1936), was approved by The Board of Education of the City of New York for circulation among

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the parents of the students:

Please answer each question with one of the following: right (R), either (E), left (L).

a. With which hand do you write?
b. With which hand do you distribute cards when dealing them?
c. With which hand do you draw or sketch a picture?
d. With which hand do you hold the top of the broom handle when sweeping?
e. With which hand do you put your house key in the keyhole when both hands are free?

Have you ever found it necessary to change your activities from one hand to the other due to illness, injury or social pressure? Yes.... No.... If the answer is yes, please give details on the other side of this questionnaire.

An introductory statement by the school authorities served to inform the parents that the study was limited to families in which both of the child's natural parents were in the home. The six schools selected as representative of the metropolitan school population distributed a total of 10,900 questionnaires. A more detailed account was presented in an earlier report (Falek, 1957).

Of the 5,652 questionnaires returned, 5,118 were acceptable for the purposes of the study. The main reasons for rejection were lack of identification, refusal to be interviewed, unavailability of the natural parent or parents because of death, failure to answer more than two questions, and impairment in the use of one hand (permanent injury or loss). School regulations precluded follow-up letters or visits to those persons who did not respond to the questionnaire.

The accepted questionnaires of each school were keyed and tabulated as to the handedness of every parent. The scoring technique for measuring an individual's hand preference on the basis of his replies to the five test items was patterned after the method used by Durost (1934). Accordingly, a person's manual dominance was determined by the difference between the number of his right (R) and left (L) responses, divided by the total number of responses. "Either" answers were counted only in the total score. Positive scores were taken to indicate various degrees of right-handedness, with negative scores denoting gradations in left-handedness.

The parent population was divided into four classes of handedness matings, the right-to-left-handed matings being subdivided according to which parent was left-handed. Since the smallest group (17 matings) was that with two left-handed parents, it was used in toto for further study. Of those matings where both parents were classified as right-handed, 20 cases were selected by random number from families where both parents scored relatively high right on the original questionnaire. From 47 families with a markedly left-handed father and 45 with a markedly left-handed mother, 20 matings were randomly selected from each group for detailed evaluation, making a total of 77 families.

Each home was visited and all family members over five years of age were tested for their hand preference by a battery of tests and personal interviews. Although all of the 77 sets of parents had previously agreed to home interview, it was only possible to complete this study on 44 of these families. On direct contact at least one of the parents in the other families refused or was unavailable for home testing.

In order to replenish the most crucial group, left-to-left matings, an additional survey was organized in another high school and in a city college. The procedure of ascertainment was simplified in such a way that instead of a questionnaire distributed among the parents, statements were read before all classes. The only item asked for was the name of any pupil both of whose parents either wrote with the left hand or both worked and ate with it. Of the 5,721 students questioned, 14 reported that both parents were left-handed. However, only nine families of this group were available for further study. Of the 53 families tested, 49 were white and 4 nonwhite. Altogether, there were 248 individuals, ranging in age from 6 to 59 years: 53 fathers, 53 mothers, 59 sons, and 83 daughters. Only the results from the home visits were used for further analysis. For the home interview all subjects were asked to demonstrate the five activities listed in the original questionnaire as well as the following four activities:

f. Hold the spoon as you do when you eat with it.
g. Strike a match.
h. Hold the knife as you do when cutting bread.
i. Thread the needle.

The family distribution for the original questionnaire and the home demonstration test is given in Table 1.

In addition to the demonstration test, a motor test battery was developed to evaluate hand preference. Previously used laterality indicators either consisted of tests of eye-hand coordination or were so designed as not to be readily transportable. There had been so much disagreement on the relation between eye and hand dominance that quantitative measures of eye-hand coordination were not used in the present study. The five tests of the motor battery to be given in the home were chosen for assessing the strength and speed of each hand, as well as index finger rapidity in wrist-arm movements, and dexterity in thumb-forefinger manipulation.

In measuring hand strength, a Kny-Scheerer dynamometer was employed in such a way that the highest score obtained in three trials by each hand was the value recorded. Because of its dimensions and ovoid shape, this test instrument proved to be difficult to manage for younger children and other persons whose fingers were too short to curl around the outer ridge.

For the remaining four tests, each hand was recorded in three intervals of five seconds each, separated by a five-second intermission. The preferred hand, as given

TABLE 1. FAMILIES CLASSIFIED AS TO HANDEDNESS OF PARENTS BY ORIGINAL QUESTIONNAIRE AND BY HOME DEMONSTRATION

Parental Mating Types			Originally Selected Population			Originally Selected Population Plus Supplementary Population	
Father		Mother	Original Quest.	Home* Q5	Home† Q9	Home* Q5	Home† Q9
R	×	R	11	15	13	16	14
R	×	L	6	4	6	8	9
L	×	R	15	19	17	21	17
L	×	L	12	6	8	8	13
Total			44	44	44	53	53

* Home retest with 5 original questions.
† With 4 additional questions.

on the questionnaire, was never tested first. The speed of the index finger was assessed by means of a tapping board, a familiar device in psychological laboratories. A Veeder-Root counter automatically recorded the number of taps produced by the right and left forefingers.

Arm-wrist movement was appraised by a "Turnbuckle Test", using a remodeled Veeder-Root counter which added each time the screw-knob was made to complete one revolution in either direction. At the signal, the knob was turned in one direction by outward wrist-arm movements with no independent activity by the fingers.

The same counter was employed in a "Watch-Winding Test". In this measure of finger dexterity, however, thumb and forefinger turned the screw-knob in an outward direction.

Wrist-hand movement was evaluated by means of a "Pencil Tapping Test". The number of pencil dots made on uniform blank sections of paper in the specified time intervals were scored at a later date.

The difference in score between the right and left hands for each of the tests of the motor battery was the raw hand preference score. A plus score indicated right-hand preference and a minus score signified left-hand preference. In the first group of families examined, retests were made after an interval of two hours. The retests were consistent and failed to reveal raw score hand preference changes in cases where the difference in score between the right and left hands was 8 or more. Subsequently, therefore, retests were made only where the difference was less than 8. Since the number of dots in the "Pencil Tapping Test" could not be counted during home visits, the size of the difference between hands was not known, and no retests were conducted.

The mean and variance of the raw hand preference scores for each of the motor tests in the six age-sex groups (fathers, sons over age 14, sons ages 6–14, mothers, daughters over age 14, daughters ages 6–14) were calculated. For the first four tests of the motor battery, the change in raw score for each hand from test to retest was used to provide data for the determination of the variance in score for each hand on retest.

Group differences in the number of tested subjects were caused by the inability of some persons, mostly youngsters, to manipulate the dynamometer or Veeder-Root counter, or sit through the Pencil Tapping Test. According to the results of an analysis of variance for the first four tests, all differences between right and left hands in the given motor measures significantly exceeded the variance for each hand upon retesting (Table 2), thus providing statistical evidence for the fact that these tests measure a characteristic which may be defined as handedness.

For the four tests administered in three parts, the relationship among these parts was studied to elicit possible effects of learning and fatigue. No significant effects were found. In the absence of such effects and in view of the agreement of test and retest, it was concluded that the motor tests were reliable.

To measure the common elements in the test battery, intercorrelations were run on the scores of the total family population, with most of them proving significant for both parents and children. In none of the six groups investigated were significantly negative correlations found for any of the tests in the battery. To the extent that the

TABLE 2. SIGNIFICANCE OF THE RATIOS OF THE VARIANCE BETWEEN HANDS TO THE VARIANCE BETWEEN TEST AND RETEST FOR ONE HAND

Motor Tests	F Values		Critical Values	
	Left Hand	Right Hand	.01	.05
Dynamometer	3.70	4.15	1.66	1.44
Finger Tap	2.47	1.82	1.45	1.32
Turnbuckle	1.78	1.43	1.43	1.29
Watch	2.39	2.07	1.39	1.26

correlations were positive, the different tests of the battery could be said to be measuring a common function.

The next step in the analysis was to combine all test scores (standard scores). For one method, the individual difference scores for each of the six tests, the five motor tests and the home demonstration, were divided by the standard deviation obtained in each test for the group under analysis: $(R - L)/s$. In another procedure, the mean score for each test in each of the six groups was subtracted from the difference scores, and then divided by the standard deviation: $[(R - L) - (\bar{R} - \bar{L})]/s$.

While the mean for the parents was close to zero, because of nearly equalized numbers in the four mating groups, that for the children was intermediate between the means for the parents and for a randomly selected group. In other words, parents and children were not directly comparable on the basis of the scores provided by the second technique. However, a difference in sign between the two sum standard scores of the motor tests for an individual proved useful as an indicator of ambidexterity. Statistically, this use of the two methods was based on the following considerations:

For the motor tests, most distributions of R−L scores were bimodal, with a mode at large positive values, more right than left, an antimode for small positive values and a second, less well-defined mode for negative values. The mean usually fell in the region of the antimode. It was assumed, then, that the antimode might be a more reasonable division point between right-hand scores and left-hand scores than would zero. Since the antimode was difficult to determine objectively, and the mean usually roughly coincided with it, it seemed that the mean might be a suitable objective, if arbitrary, cut-off point. Further, since social pressure tends toward right-handedness, individuals who were inherently right-handed were expected to have right-handed scores, while some individuals who were inherently left-handed would be shifted towards the right-hand end of the scale and have only small left-hand scores, and ambidexters would tend to be found in the group with low right-hand scores. Hence it seemed reasonable to classify all individuals with negative R − L scores as left-handed, all those with scores above the mean as right-handed, and those falling between as ambidextrous or of doubtful hand preference. While 43 of 142 children were classified as ambidextrous, only three mothers and no fathers were so classified. It should be remembered that many of the parents were selected because of their high scores.

The original questionnaire scores were used for estimating the frequency of left-handedness in the parental population (10,236 parents). In this population 3.10 per cent of the mothers and 3.88 per cent of the fathers were classified as left-handed. The difference between the sexes was not statistically significant ($.007 \pm .0037$).

In the 53 families subjected to further analysis, the 142 children have similar percentages of left-hand responses to eight of the nine questions on the home demonstration test. The only exception is the bimanual broom sweeping item, where there is a higher percentage of left responses. In the parental sample, however, left-hand scores are less frequent in response to the writing and drawing questions than to the others, apparently as a reflection of previous school pressures on the determination of hand preference.

A next step in the study is the analysis of the data by family groups. In comparing the handedness of the children of the four mating types on the demonstration test, a significant inter-group difference is found at the five per cent level ($\chi^2_{(3)} = 8.82$). Relatively low frequencies of left-handed offspring are seen in all mating categories except for that between left-handed mothers and right-handed fathers, which produces a significant increase in left-handed children (Table 3). There is no significant difference in the proportions of left-handed children when the offspring of left-handed mothers are compared with those of right-handed mothers. What is more, the frequency of left-handedness in the children of two left-handed parents does not differ statistically from that found in the children of either two right-handed parents or a left-handed father and a right-handed mother.

The motor test results present a somewhat different picture. Using the $(R - L)/s$ or $[(R - L) - (\bar{R} - \bar{L})]/s$ scores discussed above, no significant hand preference differences are obtained among the children of the four mating groups, apparently due to the fact that some individuals yielded $R - L$ difference scores close to zero. In other words, they did equally well with both hands. Such ambidextrous persons may have been easily shifted in hand preference classification by relatively small error variations in the scores.

It seemed advisable, therefore, to reanalyze the data without those individuals for whom the sum of the standardized scores calculated in the two ways given above differed in sign, indicating ambidexterity. When one of the parents was found to be ambidextrous, the entire family was omitted. There then remain 45 families with 92 children (Table 4).

Significant differences ($P < .05$) are now seen among the children of the four mating groups. In order to examine the combined results of the motor and demonstration tests in this population, the demonstration test data have been recalculated for those families and children accepted for the motor test analysis. The results again show significant inter-group differences ($P < .025$) for the offspring of the four mating groups (Table 5).

TABLE 3. COMPARISON OF HANDEDNESS OF CHILDREN ACCORDING TO PARENTAL MATINGS (DEMONSTRATION TEST)

	R. ♂ × R. ♀	R. ♂ × L. ♀	L. ♂ × R. ♀	L. ♂ × L. ♀	Total
Number of Matings	14	9	17	13	53
Right-Handed Children	36	15	41	26	118
Left-Handed Children	4	9	6	5	24
Total	40	24	47	31	142

$\chi^2_{(3)} = 8.82$, $P < .05$

TABLE 4. COMPARISON OF HANDEDNESS OF CHILDREN ACCORDING TO PARENTAL MATINGS (MOTOR TESTS: EXCLUSIVE OF AMBIDEXTERS)

	R. ♂ × R. ♀	R. ♂ × L. ♀	L. ♂ × R. ♀	L. ♂ × L. ♀	Total
Number of Matings	9	8	16	12	45
Right-Handed Children	17	8	28	18	71
Left-Handed Children	3	8	6	4	21
Total	20	16	34	22	92

$\chi^2_{(3)} = 8.18$, $P < .05$

TABLE 5. COMPARISON OF HANDEDNESS OF CHILDREN ACCORDING TO PARENTAL MATINGS (DEMONSTRATION TEST: EXCLUSIVE OF AMBIDEXTERS)

	R. ♂ × R. ♀	R. ♂ × L. ♀	L. ♂ × R. ♀	L. ♂ × L. ♀	Total
Number of Matings	11	7	16	11	45
Right-Handed Children	21	8	30	18	77
Left-Handed Children	3	6	5	1	15
Total	24	14	35	19	92

$\chi^2_{(3)} = 9.41$, $P < .025$

From Tables 3, 4 and 5 it is clear that there is a significant relationship between the handedness of the parents and the frequency of left-handed children. Interclass correlations between parental scores and those of their children, however, do not show any degree of association. The nonlinear relationship between the number of left-handed parents (0, 1, or 2) and the frequency of left-handed offspring accounts for the absence of a significant correlation between the average scores of parents and children. Furthermore, the similar frequencies of left-handed children when both parents are right-handed or left-handed indicate that hand preference is not readily explained on the basis of classical Mendelian segregation.

A plausible working hypothesis might be that hand dominance results from the interaction of the genetic potentialities of the child and various parental attitudes. The effectiveness of the guidance provided by the parents in changing any inborn preference would seem to depend on the degree of coercion used, on the age of the child at the time of parental intervention, and on the consistency with which such pressure is brought to bear on the child. This hypothesis is supported by data obtained in re-interviews with 19 cooperative families in the four parental combinations (three sets of right-handed parents, four with a left-handed father, three with a left-handed mother, and nine where both parents are left-handed).

The attitudes of the parents towards handedness may largely be the result of their own social, vocational and economic experiences. Social problems are reported by left-handed subjects of either sex. Aside from the embarrassing need for special seating arrangements at the table, many left-handed persons find their unusual hand preference used by others as the butt of unpleasant jokes. Nevertheless, social drawbacks seem to be less important as a motivating force than the vocational and economic problems faced by the left-hander.

For example, local vocational agencies report that in semi-skilled and factory employment the left-handed male has a considerable disadvantage in job placement, mainly because machines are designed for the right-hander. It is not surprising, therefore, that left-handed fathers interested in improved economic opportunities

for their children should be particularly set on having the home training directed toward right-handedness. The majority of fathers in the family study are in non-professional occupations. Of interest is the fact that children of the left-handed fathers tend to be right-handed.

The majority of mothers in our sample were employed either in secretarial or in unskilled capacities and only worked for a short time prior to marriage. Hence the left-handed mother, while experiencing social pressures similar to the left-handed father, encounters only a fraction of the economic and vocational stresses associated with hand preference. It may be for this reason that left-handed females tend to be more permissive in regard to left-handedness in their children than are their husbands. Only when they are married to left-handed husbands do they apply themselves most diligently to the task of turning their children into right-handers.

Right-handed parents are rarely familiar with the problems faced by left-handers in a right-handed world and are therefore not concerned with the hand preference of their children. With little or no parental guidance in this respect, the large majority of their children tend to become right-handed anyway. A higher frequency of left-handed children occurs only in the mating group where the father is right-handed and the mother left-handed. Without reinforcement from her husband's bias, a left-handed mother does not seem to exert much pressure on her own account in the determination of her children's hand preference.

In the group of matings where the father is left-handed and the mother right-handed, the father's bias against left-handedness is sufficiently strong to result in as low a frequency of left-handed offspring as is found in right-to-right matings. Right-handed mothers in this group become acquainted with the disadvantages of left-handedness through some of the problems encountered by their husbands. They cannot be expected, however, to be so strongly or so consistently motivated to direct the development of hand preference in their children as left-handed mothers married

TABLE 6. HANDEDNESS OF CHILDREN IN REINTERVIEWED FAMILIES

Parental Mating Types			Occupation of Father	Children					
				Little Home Pressure		Moderate Home Pressure		Constant Home Pressure	
Father		Mother		R	L	R	L	R	L
R	×	R (3)	Laborer	2	—	—	—	—	—
			Semi Prof.	—	1	—	—	—	—
			Professional	1	1	—	—	—	—
R	×	L (3)	Laborer	5	1	—	—	—	—
			Semi Prof.	1	2	—	—	—	—
			Professional	—	—	—	—	—	—
L	×	R (4)	Laborer	—	—	—	—	8	—
			Semi Prof.	—	—	3	—	—	—
			Professional	2	1	—	—	—	—
L	×	L (9)	Laborer	—	—	—	—	7	1
			Semi Prof.	1	—	—	—	5	—
			Professional	1	1	—	—	2	2

to left-handed fathers. In fact, there is evidence from the re-interviews that they do not exert as much pressure (Table 6).

On this basis, it may be hypothesized that dissimilar degrees of parental influence mask the original difference between the innate potentialities of children of left-handed fathers and right-handed mothers and of children of two left-handed parents. As a result, equal frequencies of left-handed children are found in these two mating groups.

Tentative support for a hereditary component in the causation of a particular hand preference comes from a combination of findings, each of which in itself would seem to carry relatively little weight. Taken together, however, these findings present a picture which supports a hypothesized genetic component of handedness. One such finding is that there are left-handed children, reported as being well-adjusted by both home and school, who remain left-handed despite the efforts of their left-handed parents to render them right-handed. It would seem, therefore, that handedness depends in part on some basic characteristic of the individual.

Another important point can be seen when one compares the frequencies of left-handed children from the two mating types where relatively little parental pressure is exerted (namely, both parents right-handed and left-handed mothers married to right-handed fathers). In the latter instance, there is a significantly higher frequency of left-handed children. The two mating groups with little parental pressure lend some indirect support to the hypothesis of a hereditary component operating in the determination of hand preference.

Finally, the parents were asked about the occurrence of left-handedness in their parents and sibs. In families with a left-handed child, the proportion of families with at least one left-handed relative was found to be significantly greater ($P < .001$) than in families with no left-handed child. The excess of families with left-handers, in the presence of a left-handed child, was so pronounced that it did not seem possible to ascribe it entirely to differences in the degree of familiarity with the handedness patterns of relatives. (Table 7).

The failure of families with a left-handed child to show a significant increase in left-handed parents does not invalidate the explanation. The results of this analysis

TABLE 7. HANDEDNESS OF RELATIVES OF PARENTS IN LEFT- AND RIGHT- CHILD FAMILIES

	Families with at least one left-handed relative	Families with no left-handed relative
Families with at least one left-handed child	15	7
Families with no left-handed child	6	25

$\chi^2_{(1)} = 10.86$, $P < .001$

TABLE 8. HANDEDNESS OF PARENTS IN LEFT- AND RIGHT- CHILD FAMILIES

	Families with a left-handed parent	Families with no left-handed parent
Families with a left-handed child	18	4
Families with no left-handed child	21	10

$\chi^2_{(1)} = 0.682$, $P < .30$

giving a P between .3 and .5 are in part explained by the fact that the left-handed fathers may have been particularly anxious to direct their children toward right-handness (Table 8).

SUMMARY AND CONCLUSIONS

In this study of the families of a representative series of New York City school children, the main objectives were to determine the mechanisms involved in the development of a hand preference in individuals, and to establish, if possible, a family pattern of hand dominance which would explain the distribution of right- and left-handedness in the children of four types of parental combination. A battery of motor and demonstration tests was used for measuring hand preference, and a sample of parents from the four mating groups was interviewed concerning the degree to which they tried to make their children right-handed.

The following conclusions were reached:

1. A consistent and statistically significant increase in the proportion of left-handed children is found only in matings of right-handed fathers and left-handed mothers. In all other mating groups (two right-handed parents, left-handed father and right-handed mother, and two left-handed parents), the observed left-handedness rates of the children vary only from 11 to 18 per cent.

2. Families differ in whether and to what extent the children are guided towards right-handedness. Left-handed fathers are particularly cognizant of the economic as well as the social drawbacks of left-handedness, and tend to be most concerned with making their children right-handed. Mothers generally cooperate with the efforts of their left-handed husbands to make their children right-handed. Compared with right-handed mothers, however, left-handed mothers are more consistent in their determination to direct their children toward right-handedness. Left-handed wives of right-handed men apparently exert little influence on the hand preference of their children. Right-handed parents are usually least aware of the problems associated with left-handedness.

3. A possible genetic effect is demonstrated by the following observations: (a) inability of some left-handed parents to change the hand preference of their children, (b) differences in the frequency of left-handed children in the two mating groups revealing no evidence of marked parental pressure, and (c) increased frequency of a left-handed relative in families with a left-handed child.

4. The hand preference of an individual is the result of both his genetic endowment and his early training in the home.

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Human Chromosome Complements in Normal Somatic Cells in Culture

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THE STUDY OF HUMAN CHROMOSOMES has received considerable attention and interest in recent years especially since the discovery of a new diploid chromosome number—46 (Tjio and Levan, 1956; Ford and Hamerton, 1956) and subsequent reports of the possible existence of chromosome number variation in man (Kodani, 1957a, b; 1958a, b). In view of the significance of the problem, the need for independent observations on various human populations is apparent. Furthermore, detailed information on human chromosome cytology appears essential in connection with experimental cytogenetical studies of human cells *in vitro* involving such problems as mutation, genetic recombination, chromosome structural changes induced by physical and chemical agents, and carcinogenesis.

In the course of studies in this laboratory using tissue culture techniques for an analysis of radiation-induced aberrations in human chromosomes, biopsy materials from a number of human individuals have been established in culture. The present paper reports the results of chromosome number determinations in these materials. In addition, a detailed analysis is presented of the human karyotype based on studies of the chromosome complements of these normal human somatic cells.

MATERIALS AND METHODS

Source of materials.—Surgical biopsies and fetal tissues from a number of human subjects have been obtained through the kind cooperation of members of the Departments of Surgery, Obstetrics and Gynecology, and Internal Medicine at the Yale University School of Medicine. Table 1 lists these materials in terms of the specimen number, tissue of origin, and sex, age, and race of the individuals involved. Most individuals, especially the new-born babies and young children, were normal and healthy. Specimen Y7 was from a woman with idiopathic thrombocytopenic purpura. Histological study of this splenic biopsy showed normal morphology. The bone marrow specimen Y9 was from a rib removed during thoracic surgery. Specimens Y15 and Y24 were from kidneys removed because of hydronephrosis; specimen Y16 came from a testicular biopsy involving a patient diagnosed with retroperitoneal lymphosarcoma. In this case, aspermatogenesis persisted for a brief period following radiation therapy. The biopsy was obtained after apparent recovery and after the man had fathered a child. Parallel histological and cytological studies indicated normal

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TABLE 1. A SURVEY OF HUMAN SOMATIC CHROMOSOME NUMBERS BASED ON CELLS IN TISSUE CULTURES FROM 34 DIFFERENT INDIVIDUALS

Specimen No.	Source	Sex and age of individual	Race[a]	Chromosome number of apparently intact diploid cells		
				45	46	47
Y 7	spleen	F, 58	W		2	
Y 9	bone marrow	F, 63	W		8	
Y 13	tonsil	M, 6	W		6	
Y 15	kidney	F, 21	W		97[b]	
Y 16	testicular fibroblast	M, 34	W		20	
	spermatocyte	"			4	
—	muscle (Sloan-Kettering)	sex unknown, embryonic	unknown		3	
—	thyroid (Tulane)	male pseudo-hermaphrodite, 28	W		8	1
Y 24	kidney	M, 75	W		12[b]	
Y 25	skin-muscle	M, 2 month embryo	W	1	76[b]	
	kidney	"			2	
	lung	"			12	
Y 32	foreskin	M, new born	W		1	
Y 33	foreskin	M, new born	N		3	
Y 34	foreskin	M, new born	W		37	4[c]
Y 40	foreskin	M, new born	W	2	10	
Y 41	foreskin	M, new born	N		22	
Y 45	foreskin	M, new born	W		13	
Y 46	foreskin	M, new born	W		15	
Y 47	foreskin	M, new born	W		10	
Y 49	foreskin	M, new born	N		17	
Y 58	foreskin	M, new born	W		5	
Y 60	foreskin	M, new born	W		18	
Y 66	bone marrow	M, 82	W		8	
Y 86	foreskin	M, new born	W		6	
Y 89	foreskin	M, new born	W		28[b]	1
Y 90	foreskin	M, new born	W		9	
Y 91	foreskin	M, new born	W		2	
Y 93	foreskin	M, new born	W		7	
Y 115	foreskin	M, new born	W		24	
Y 117	foreskin	M, new born	W		31	
Y 121	foreskin	M, new born	W		17	
Y 128	foreskin	M, new born	W		20	
Y 140	foreskin	M, new born	N		9[b]	
Y 141	foreskin	M, new born	W		12	
Y 144	foreskin	M, new born	W		4	
Y 148	foreskin	M, new born	W		33	

a) W (American Whites); N (American Negroes).
b) includes 1 to 3 cells having 46 diplochromosomes.
c) see text for discussion of these counts.

morphology and spermatogenesis. The bone marrow specimen Y66 was taken by ilium puncture from a man with pernicious anemia.

The embryonic muscle cell culture was obtained from the laboratory of Dr. Alice E. Moore, Sloan-Kettering Institute for Cancer Research, New York City. The thy-

roid culture was initiated in the laboratory of Dr. William Sternberg at the School of Medicine, Tulane University, New Orleans, Louisiana. It came from a thyroid biopsy involving a 28 year old male pseudohermaphrodite in a family studied genetically by Dr. Sternberg and Dr. H. W. Kloepfer of the same University. The generous cooperation of the Yale Medical staff and of others who supplied materials is gratefully acknowledged.

Tissue-culture techniques.—Immediately after removal, tissue specimens were placed in sterile moist containers including a gauze soaked with physiological saline (Ringer's solution). The bone marrow specimens were injected first into a vial containing Hanks' balanced saline with heparin (1:20,000). The specimens were either cultured immediately or stored at 4° C for a few hours to overnight before culturing.

In establishing cultures, the specimens were first rinsed with Hanks' balanced saline at room temperature, cut into pieces of 1–2 mm^3 in size, and trypsinized according to the method of Rappaport (1956). For cell dissociation, 0.2 per cent trypsin (Difco 1:250) in phosphate-buffered (Na_2HPO_4—KH_2PO_4) saline was generally used. Trypsinization was continued for 5–10 minutes with embryonic materials and for 30–60 minutes with other materials after which a sample of cell suspension was taken for microscopic examination and cell counts in a hemacytometer. The cells were then centrifuged and resuspended in growth medium. For bone marrow, the cells were centrifuged directly and resuspended in growth medium.

The growth medium used contained 75 per cent Eagle's synthetic supplement (Eagle, 1955; Eagle *et al*, 1956), 20% non-pooled human serum (Obtained from the Philadelphia Serum Exchange, 1740 Bainbridge Street, Philadelphia, Pennsylvania.) with blood type predetermined and 5 per cent beef embryo extract ultrafiltrate (Obtained from Microbiological Associates, Inc., Bethesda, Maryland.).

A cell suspension of 1–3 $\times$ 10^5 cells per ml. was inoculated into either 3 oz. prescription bottles or depression test tubes (Leighton tubes) containing removable clean sterile 30 x 11 mm cover slips, and incubated at 37° C. Viable cells settled within 12 hours and began to proliferate on glass. The medium was changed after two to three days. In about a week when the cell population in culture bottles had increased approximately 5 to 10 fold, the cells were dissociated by means of trypsinization and subcultured in the same medium.

It is often desirable to test each individual batch of serum before use for a particular cell line, since serum toxicity of unknown nature may affect cell growth or cause undesirable cellular and chromosomal alterations. Although most tissues are potentially capable of initiating cell proliferation *in vitro*, not every biopsy specimen was established as a cell line with active growth. Growth rates also vary in different cases. Cytological studies were made as soon as feasible, usually at the second transfer—about one week after the initiation of a culture. However, many cell lines were reasonably stable and exhibited no obvious cellular or chromosomal alterations after three to six months in culture. Morphologically, most cells were fibroblast-like, but the cells from kidney cultures were epithelium-like.

Cytological techniques.—The general procedure in preparing slides for chromosome studies was similar, with a few modifications, to that previously described (Chu and Giles, 1957, 1958a). In order to accumulate metaphases, colchicine pretreatment was employed. A final colchicine concentration of 10^{-6} gm. per l. was incorporated into

the culture medium 2–5 hours before fixation. Chromosome spreading was achieved by incubation of cells on cover slips in hypotonic saline (5 per cent full formula Hanks' with 95 per cent Hanks' minus NaCl) at 37° C for 15 to 20 minutes. The cells were then fix-stained by inverting the cover slip over a drop of aceto-orcein (1 per cent of natural orcein (Obtained from G. T. Gurr, Ltd., London, England.) in 45 per cent acetic acid containing 2 per cent by volume of 1N HCl) on a clean slide. The preparation was placed between layers of bibulous paper and pressed very lightly. It was then either sealed with Krönig cement (Obtained from Riedel-de Haën AG. Seelze bei Hannover, Germany.) as a temporary preparation or rendered permanent by the following procedure: the preparation was dipped in liquid nitrogen for 3–5 seconds; the cover slip was carefully separated from the slide by prying off with a razor blade; dehydration and clearing followed by passing both the slide and cover slip through a series of baths—(1) pre-chilled 1:1 acetone-tertiary butyl alcohol (TBA) for 30 min. at −10° C (in freezer compartment of a refrigerator), (2) TBA containing 1 per cent 1N HCl for 15 sec. at room temperature, (3) 1:1 xylene-TBA for 1–2 min., and (4) two successive xylene baths for 2 min. each; the preparation was then mounted in Canada balsam.

Chromosome studies.—Chromosome counts, idiogram analyses, and photomicrographs were made in the same manner as previously described (Chu and Giles, 1958a). All chromosome counts were exact counts from single intact cells. Chromosome measurements were made either from camera lucida drawings of individually centered chromosomes or from enlarged prints (ca 3000×). Measurements were estimated to the nearest 0.5 mm of a metric ruler and recorded as "units". Standard errors were calculated and the significance of differences tested at the 95 per cent level of fiducial probability.

RESULTS

Chromosome number.—Somatic chromosome counts have been made of cells in culture derived from 34 different human subjects (Table 1). Regardless of race, sex, age, or tissue, in all cases the diploid chromosome number was 46. In one individual (Y16), 4 primary spermatocytes were analysed in which 23 pairs of chromosomes were clearly seen at metaphase I. This is in agreement with the diploid chromosome number determined in testicular fibroblasts *in vitro* derived from the same individual. In one of the fetuses (Y25) chromosome counts were the same in cells derived from skin-muscle of a fore limb, kidney, and lung. Of particular interest is the case of a male pseudohermaphrodite. Buccal cell smear preparations were sex chromatin-negative indicating the presumptive genetic sex as male. In agreement with this observation, chromosome determinations using thyroid biopsy material grown *in vitro* showed that this individual has 46 chromosome including an X and a Y chromosome.

In a few exceptional cells, deviations of one chromosome from normal were observed. These counts may represent either instances of somatic aneuploidy, originally present or induced during cultivation, or artifacts resulting from errors in technique. In one instance, Y34, an actual chromosome number alteration was observed during cultivation. Among 29 cells analyzed at the fourth transfer—two weeks

after the initiation of the culture—only one cell was suspected of having an extra chromosome. Later at the ninth transfer (after nearly three months in culture) three such cells were found among an additional 12 cells examined. The extra chromosome had a submedian centromere, and was approximately the size of chromosome number 8 (see below). The chromosomes in the normal complement showed no visible change.

In some cultures tetraploid cells and cells with diplochromosomes were present in which exact chromosome counts were possible. The overall frequencies of these cells was well below 5 per cent. The results of chromosome counts in such cells confirmed the basic diploid number, i.e., 46.

Chromosome morphology.—Representative photomicrographs of human chromosomes from individual somatic cells in culture are presented in Figures 1 and 2. Camera lucida drawings of five additional cells derived from different individuals of both sexes are shown in Figures 3 and 4. Homologous chromosomes and the sex pair were identified initially by chromosome matching and then more accurately by measurements. The method of Rothfels and Siminovitch (1958) for identification of homologous chromosomes was employed. The total length and arm lengths of each chromosome were measured and the arm index calculated by dividing the length of the short arm into that of the long arm. Utilizing these data, homologues were convincingly paired in each individual cell. The X and Y chromosomes were first recognized in male cells and the pair of X chromosomes then identified in female cells. There was no evidence of chromosomal heteromorphism among the autosomes.

At metaphase, the longest chromosome measures from 8 to 10 microns, and the smallest, the Y, from 1.2 to 1.5 microns. Since the length of a chromosome depends on the state of condensation and is also affected by the colchicine treatment employed in these studies, it is desirable to express relative lengths in terms of percentage of the haploid complement. Furthermore, in order to avoid the differences between sexes, these percentages were calculated on the basis of total autosome length only. In Table 2, the relative lengths of individual human chromosomes are expressed in terms of their mean percentage of the total length of the haploid autosomal complement calculated from measurements of one female cell and three male cells from different individuals, i.e., the average of eight homologous chromosomes. The mean arm index of all chromosomes, based on measurements from these and three additional male cells each from a different individual, is also included. It is evident that every pair of homologous chromosomes of the human complement can be individually recognized. Furthermore, appropriate statistical tests show that homologous autosomes from cells of the same or of different individuals do not differ significantly either in relative length or in centromere position. The only difference between chromosome complements of the two sexes resides in the sex chromosomes. Similarly, there are no significant differences among the X chromosomes or among the Y chromosomes from different individuals.

An idiogram of the human karyotype (Fig. 5) has been constructed on the basis of the above results. The chromosomes of the haploid set are arranged in order of decreasing lengths, following the classical procedure. If two chromosomes are of equal length, the one with the more nearly median centromere is placed first. Arabic

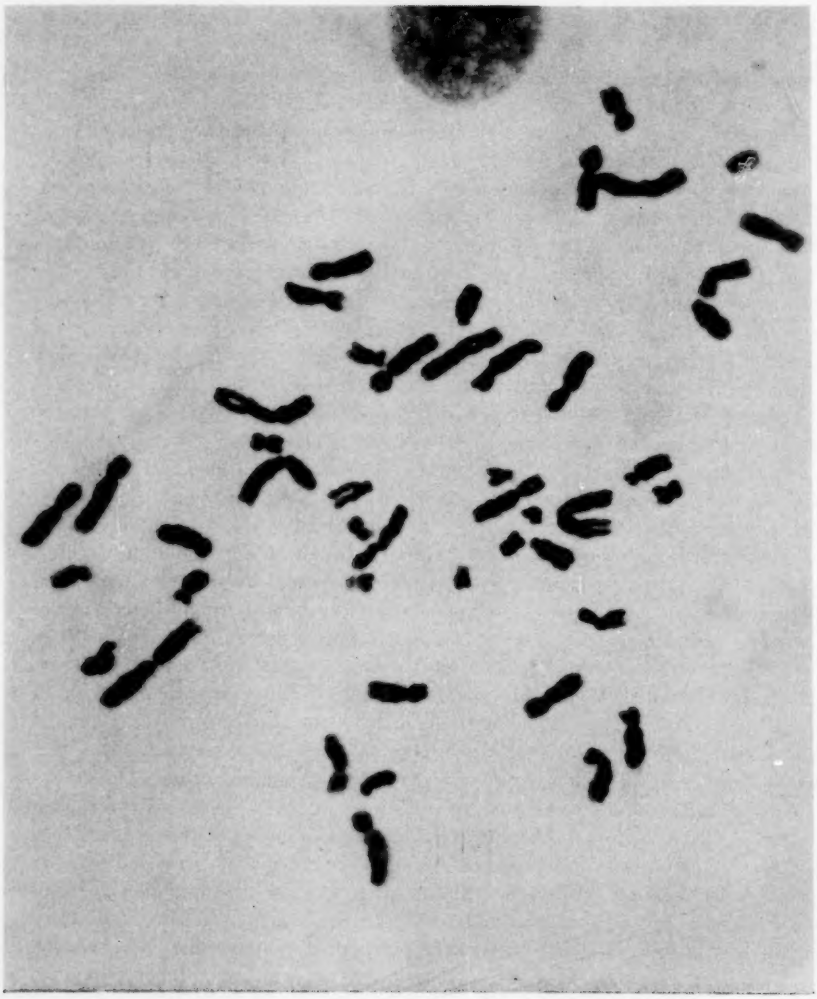

FIG. 1. Normal diploid complement (2n = 46) of a cell in a culture derived by foreskin biopsy (specimen Y 89) from a new born White male. Acetoorcein stain. 2100×.

FIG. 1. Normal diploid complement (2n = 46) of a cell in a culture derived by foreskin biopsy (specimen Y 89) from a new born White male. Acetoorcein stain. 2100×.

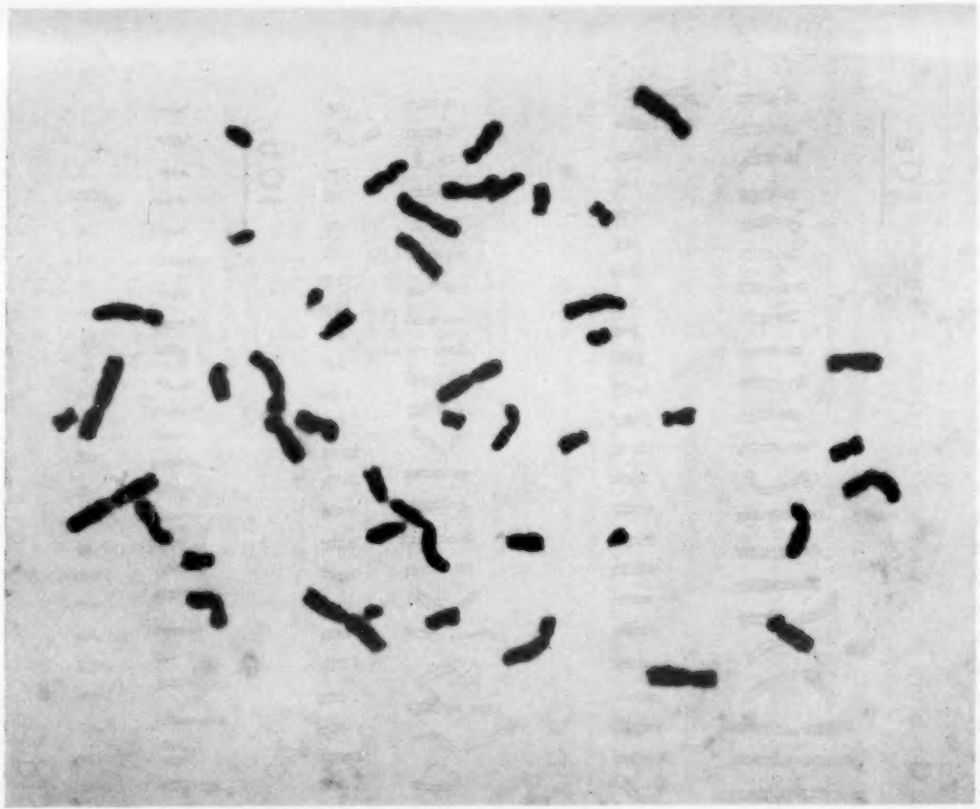

FIG. 2. Normal diploid complement (2n = 46) of a cell in a culture derived by bone marrow biopsy (specimen Y 66) from an 82 year old White male. Acetoorcein stain. 1800×.

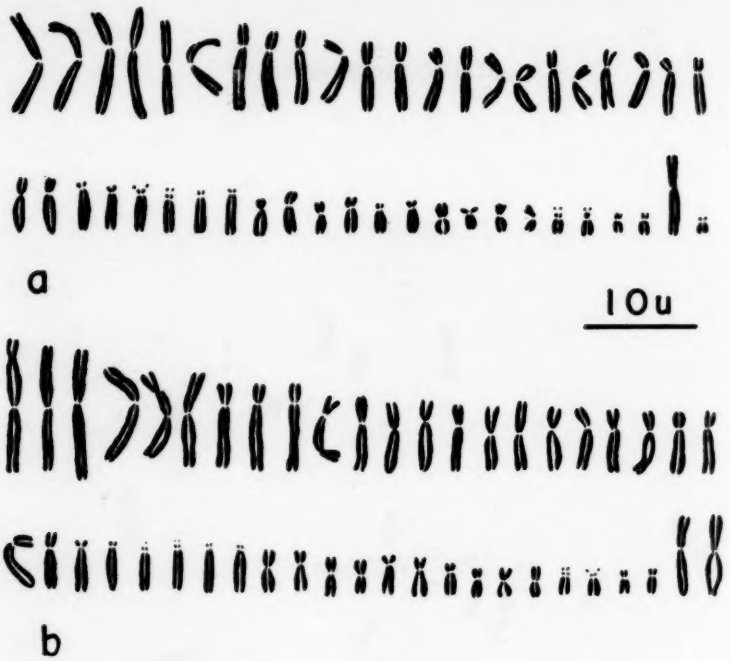

FIG. 3

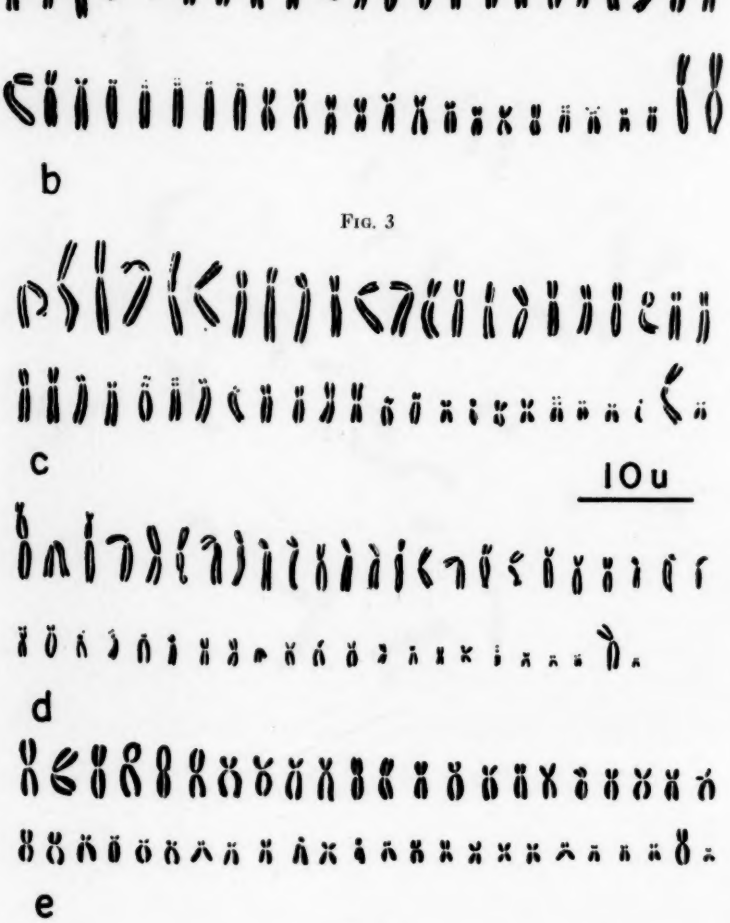

FIG. 4

FIGS. 3 and 4. Idiograms of human diploid cells growing *in vitro* derived from five separate individuals as follows: a. skin-muscle (specimen Y 25), male; b. kidney (specimen Y 15), female; c. foreskin (specimen Y 89), male; d. foreskin (specimen Y 34), male; and e. foreskin (specimen Y 45), male.

numerals have been used to designate individual autosomes. The sex chromosomes, X and Y, are placed last.

Using the system of Tjio and Levan (1956) the chromosomes have been classified into 3 groups: M chromosomes (median-submedian centromeres), S chromosomes (subterminal centromeres) and A chromosomes (acrocentric chromosomes—those chromosomes having nearly terminal centromeres) (Table 2). On this basis, the human diploid chromosome complement consists of 9 pairs of M, 8 pairs of S, and 5 pairs of A autosomes in addition to the sex pair. The Y chromosome is acrocentric. In addition to the method just described, certain members of the complement have characteristic morphological features which aid in individual chromosome identification.

To facilitate description and identification, human somatic chromosomes can be arranged in 7 "natural" sub-groups (Table 3) as follows:

I. The five longest chromosomes can be easily and unequivocally recognized. Chromosomes 1, 2, and 3 are M chromosomes while 4 and 5 are S chromosomes.

TABLE 2. CHARACTERIZATION OF HUMAN CHROMOSOMES IN TERMS OF LENGTH AND ARM INDEX. THE RELATIVE LENGTHS OF INDIVIDUAL CHROMOSOMES ARE EXPRESSED IN TERMS OF THEIR MEAN PERCENTAGE OF THE HAPLOID AUTOSOMAL COMPLEMENT. ARM INDICES WERE DETERMINED FOR EACH CHROMOSOME BY DIVIDING THE LENGTH OF THE SHORT ARM INTO THAT OF THE LONG ARM. FOR FURTHER DETAILS, SEE TEXT.

Chromosome designation	Mean percent haploid autosomal complement	Mean arm index	Position of centromere†
1	9.53 ± 0.02*	1.07 ± 0.00*	M
2	9.15 ± 0.05	1.48 ± 0.01	M
3	7.60 ± 0.14	1.16 ± 0.01	M
4	6.57 ± 0.30	2.89 ± 0.03	S
5	6.10 ± 0.05	3.17 ± 0.22	S
6	5.88 ± 0.10	1.77 ± 0.07	M
7	5.45 ± 0.03	1.89 ± 0.10	M
8	4.90 ± 0.00	1.65 ± 0.07	M
9	4.90 ± 0.00	2.40 ± 0.23	S
10	4.72 ± 0.00	2.31 ± 0.12	S
11	4.55 ± 0.03	2.12 ± 0.10	S
12	4.46 ± 0.05	3.13 ± 0.31	S
13	3.60 ± 0.03	9.53 ± 0.57	A
14	3.43 ± 0.04	9.67 ± 0.27	A
15	3.34 ± 0.06	11.94 ± 1.80	A
16	3.17 ± 0.04	2.07 ± 0.04	S
17	2.79 ± 0.06	1.60 ± 0.06	M
18	2.58 ± 0.04	3.75 ± 0.43	S
19	2.32 ± 0.09	1.95 ± 0.18	M (S)
20	2.02 ± 0.06	1.28 ± 0.03	M
21	1.59 ± 0.08	6.83 ± 0.17	A
22	1.25 ± 0.06	6.00 ± 0.00	A
X		2.05 ± 0.14	S (M)
Y		5.00 ± 0.00	A

* 95% level of fiducial probability.

† M (median and submedian); S (subterminal); A (acrocentric).

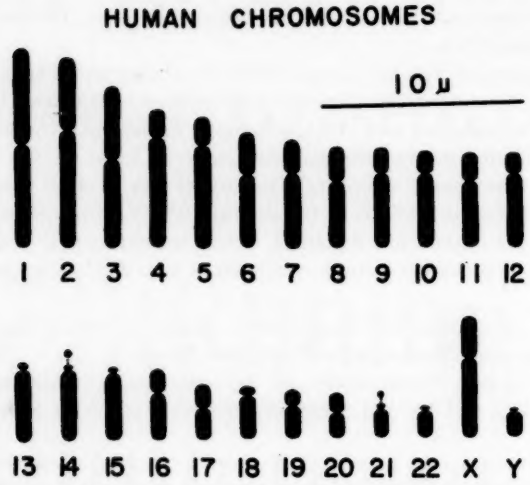

FIG. 5. Idiogram of the human haploid chromosome complement, including the sex pair. The autosomes are arranged in order of decreasing total length and of relative centromere positions. If two chromosomes are of equal length, the one having the more nearly median centromere is placed first.

TABLE 3. HUMAN SOMATIC CHROMOSOMES GROUPED TO FACILITATE IDENTIFICATION. FOR FURTHER DETAILS, SEE TEXT.

Group Designation	Chromosome classification on basis of centromere position*		
	M	S	A
I	1, 2, 3	4, 5	
II	6, 7, 8	X	
III		9, 10, 11, 12	
IV			13, 14, 15
V	17	16, 18	
VI	19, 20		
VII			21, 22, Y

* M (median and submedian); S (subterminal); A (acrocentric)

II. The X chromosome is about the same length as chromosome 5 but with a more median centromere. Chromosomes 6, 7, and 8 are M chromosomes, shorter than the X, but not easily distinguishable from each other without actual measurements.

III. Chromosomes 9 to 12 represent the most difficult group of all for individual chromosome identification, although all are clearly S types.

IV. The three pairs 13 to 15 are acrocentric chromosomes, and are clearly shorter than the chromosomes of group III. The shorter arm of chromosome 13 appears to be longer than the shorter arms of the other two chromosomes in the group. Chromosome 14 has a small satellite on the shorter arm. Tjio and Puck (1958) have recently

reported heterozygosity with respect to the size of the satellites of this chromosome pair in cells of two female individuals.

V. This group includes 3 chromosomes (16, 17, and 18) which are easily distinguishable from each other. In length, chromosome 16 approaches the acrocentric chromosome 15. Chromosome 17 is the only M chromosome in this group; chromosome 18 has a subterminal centromere.

VI. This group contains chromosomes 19 and 20, the latter being particularly easy to identify in the complement because of its size and its nearly median centromere.

VII. This final group includes two pairs of small acrocentric chromosomes, and the Y chromosome in the case of male cells. Chromosome 21 has a small satellite, com-

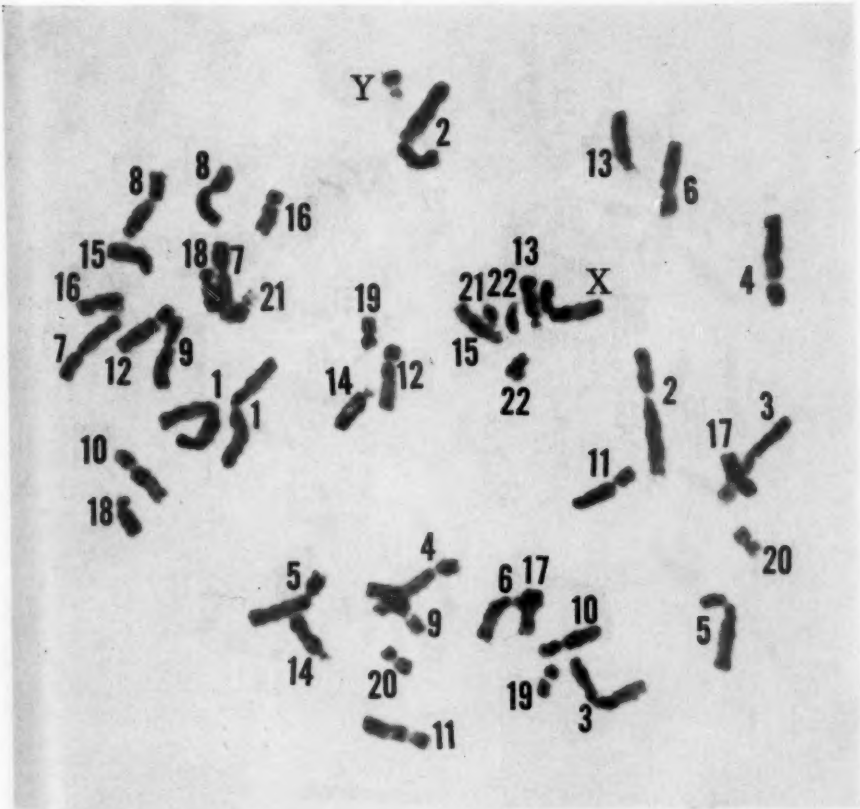

FIG. 6. Normal diploid complement (2n = 46) of a cell at metaphase in a culture derived by foreskin biopsy (specimen Y 89) from a new born White male. All chromosomes have been identified by number (cf. figure 5). Acetoorcein stain. 2150×.

parable in morphology to that of chromosome 14, on its shorter arm. Chromosome 22 is acrocentric, smaller than 21, and without a satellite.

The Y chromosome is apparently the smallest in the whole complement, but differs very little in length from chromosome 22. In most figures it also appears to be acrocentric, not telocentric. The presence or absence in the somatic complement of this fifth small acrocentric chromosome has been successfully used to diagnose the sex of the individual from whom cells have been derived (Ford, Jacobs and Lajtha, 1958).

Figures 6 and 7 present two photomicrographs—one of a male and the other of a female cell—in which all chromosomes have been identified on the basis of the criteria just described and are individually labelled. Figure 8 shows another female cell in which the four satellited chromosomes are indicated.

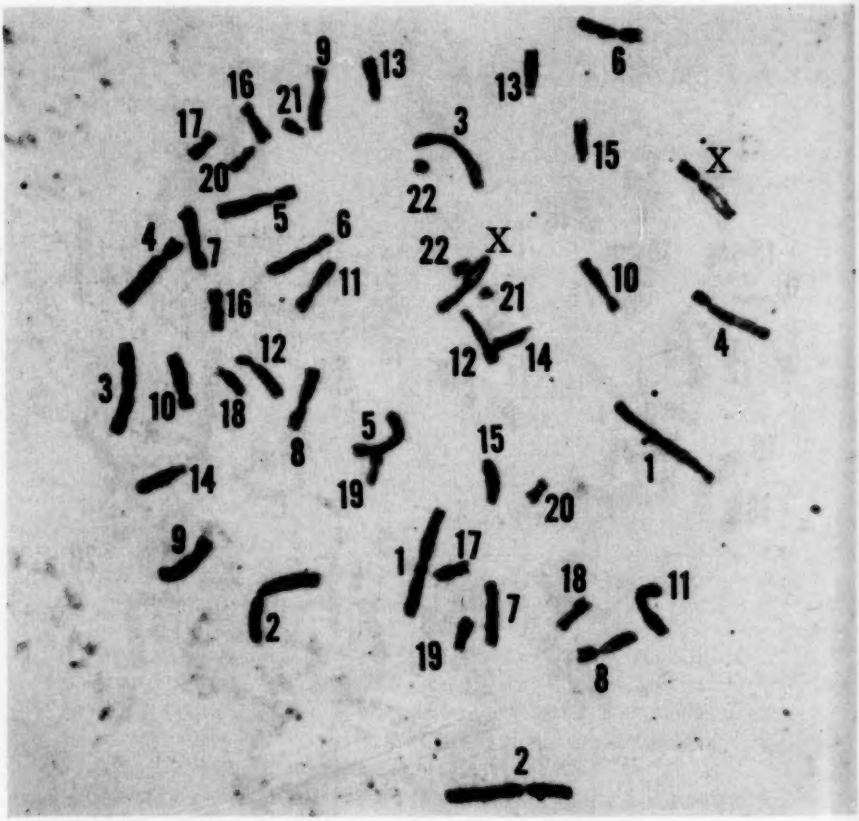

FIG. 7. Normal diploid complement (2n = 46) of a cell at early metaphase in a culture derived by kidney biopsy (specimen Y 15) from a 21 year old White female. All chromosomes have been identified by number (cf. figure 5). Acetoorcein stain. 1650×.

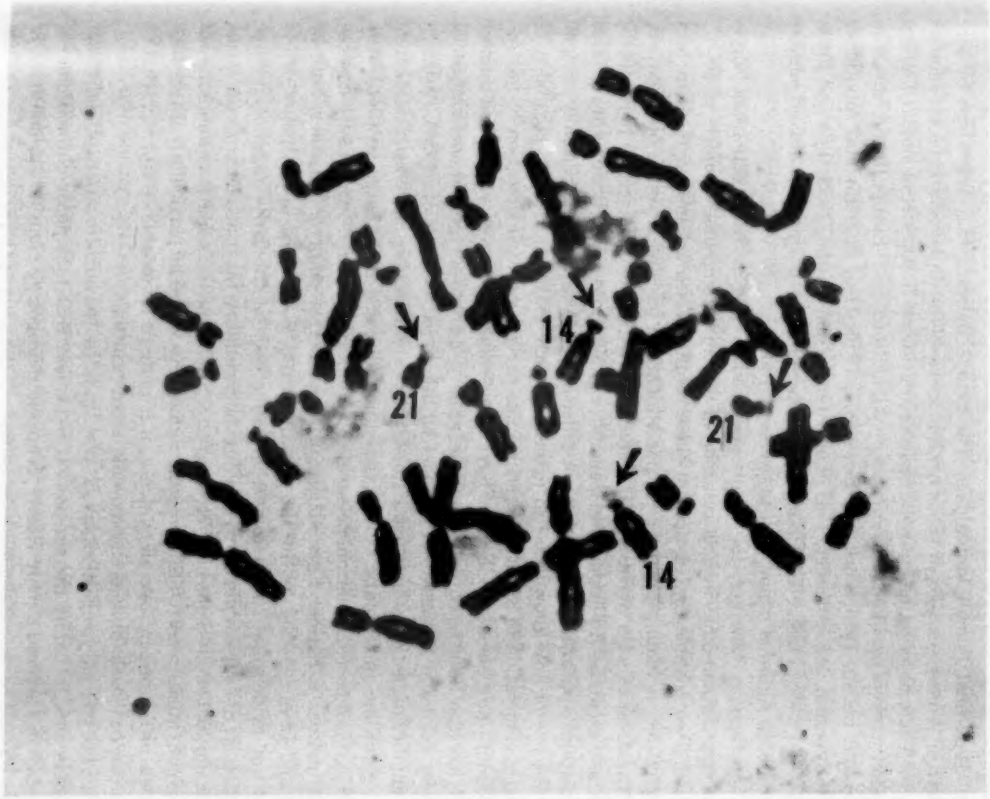

FIG. 8. Another cell from the same individual as in figure 7. This preparation shows the four chromosomes (labelled as two 14's and two 21's) having satellites (indicated by arrows) on their shorter arms. Acetoorcein stain. 2950×.

DISCUSSION

With the application of tissue culture and suitable cytological techniques, information has been obtained on chromosome number and morphology in somatic cells from 34 normal human individuals. The results indicate that regardless of race (Negro or White), sex, age, or tissue used, in all cases the diploid chromosome number was 46. These observations provide additional evidence in support of similar findings by other workers based on different human populations, both European and American (Tjio and Levan, 1956; Ford and Hamerton, 1956; Hsu, Pomerat and Moorhead, 1957; Syverton, 1957; Bender, 1957; Ford, Jacobs and Lajtha, 1958; Tjio and Puck, 1958; Tjio, 1958; Puck, 1958.) The total number of cases in which the diploid number 46 has been recorded is now well in excess of 100.

There remain, however, the reports by Kodani (1957a, b; 1958a, b) of supernumerary chromosomes in man resulting in diploid chromosome numbers of 46, 47, and 48. Two possible explanations of these results, which are in disagreement with all other recent findings, may be considered. On the basis of Kodani's observations, supernumeraries seem to occur with a much higher frequency in certain populations, such as Orientals. Additional independent examinations of individuals from these populations appear highly desirable in order to clarify this point. Secondly, despite the absence of any known case in mammals, there exists the remote possibility of somatic elimination of supernumeraries, thus preventing their detection in individuals from whom somatic cells alone have been studied. However, the diploid number of 46 has also been repeatedly found in primary spermatocytes and spermatogonial cells by Ford and Hamerton (1956) and by others (cf. Ford, *et al.*, 1958). Although the number of instances in which chromosome determinations have been made from both germ line and somatic cells of the same individual is not large, available data (Y16 in this report; Hamerton, personal communication) do not suggest such chromosome number variation. Examination of a number of embryonic tissues, both by Tjio and Levan (1956) and by the present writers as reported in this paper, fail to show any evidence of chromosome elimination even at the early stages of development. It is, of course, difficult to rule out the possibility that such elimination occurs at the initial cell divisions of a fertilized egg. Studies of the somatic chromosomes of those individuals reported to have supernumeraries would be particularly interesting. In view of the present overall evidence, it is perhaps reasonable to conclude that 46 is the correct basic diploid chromosome number in man.

The present karyological analysis also leads to the identification of individual chromosomes, including the sex pair. It is evident that metaphase chromosomes in somatic cells assume a more clearly definable morphology than do chromosomes in either meiotic or spermatogonial metaphases. Somatic cells in tissue culture provide additional advantages in having increased mitotic activities and in permitting more efficient cytological treatments. On the basis of detailed microscopical comparisons and actual measurements, an idiogram of the human karyotype has been constructed. This idiogram is in general agreement with the idiograms presented by Hsu (1952) and more recently by Ford *et al.* (1958) and by Tjio (1958). The present idiogram is also roughly comparable to the one proposed by Kodani (1957a) based on measurements of meiotic first metaphase chromosomes and to another by the same author

(1958b) in which relative chromosome arm lengths of certain chromosomes can be inferred on the basis of the pairing configurations of bivalents at the meiotic metaphase.

Statistical analysis has established that there are no significant differences in the morphology of individual chromosomes (based on determinations of relative lengths and arm indices) among several individuals examined in this study. The human sex chromosomes are heteromorphic, but there are no morphological differences among X chromosomes or among Y chromosomes derived from different individuals. Since this idiogram is in general agreement with those prepared by others, this conclusion on chromosome morphological constancy is probably generally true. The heterozygosity of satellites on chromosome 14 (Tjio and Puck, 1958) has not been observed in the present group of samples.

The occurrence of pronounced heteromorphy in the human sex chromosomes has important implications for such phenomena as the mechanism of sex determination, sex linkage, and the cytological diagnosis of sex. On the basis of somatic length the X chromosome is 4 to 5 times longer than the Y. Heterochromaticity has been reported to occur in the entire shorter arm of the X (Kodani, 1957a) and in a fairly large region close to the centric end of the Y (Tjio and Puck, 1958). During meiosis, Sachs (1954) has noted the absence of normal pairing between the X and Y. In addition, Kodani (1957a) has found that the X and Y associate at meiosis in only 60% of the cells. When they do pair, the region of association is limited to the tips of shorter arms of the two chromosomes. The great difference in total length, the presence of long heterochromatic regions, the limitation of pairing regions, and the high frequency of nonconjugation all lead to the conclusion that there is little if any homology between the human X and Y chromosomes.

The presence or absence of a Y chromosome can be used to diagnose the genetic sex of cells (Hsu *et al.* 1953). This procedure is particularly useful as a direct test of the validity of the diagnosis of the genetic sex of intersexual individuals on the basis of the presence or absence of "sex chromatin" (Barr *et al*, 1950; Moore *et al*, 1953). The study by Ford *et al.* (1958) on a case of Klinefelter's syndrome and the present report on a male pseudohermaphrodite are cases in point. In both instances, the diagnosis of genetic sex by means of the sex chromatin method was verified by direct chromosome examination.

The pronounced heteromorphy of the human XY chromosome pair would also appear to provide a likely cytological explanation for the distinction between female and male cells based on sex chromatin. It is evident that the major cytological difference between cells of the two sexes resides in this heteromorphic pair of chromosomes. Since the X is much larger than the Y and its entire shorter arm is reported to be heterochromatic (Kodani, 1957a), a reasonable hypothesis appears to be that sex chromatin represents the heterochromatic region of the X chromosome and regularly appears only when both X chromosomes are present in a female cell. Evidence in support of this hypothesis has been reported by Reitalu (1957).

Finally, the two pairs of autosomes with satellites (chromosomes 14 and 21) are probably nucleolus-organizing chromosomes. The finding (Chu and Giles, 1958b) that the human somatic interphase nucleus contains basically four spherical nucleoli—

one large and one small pair—supports this view. Detailed cytological studies of the nucleolar constitution of human somatic cells will be published later.

SUMMARY

Studies have been made on chromosome number and morphology in somatic cells in tissue cultures derived from 34 normal human subjects including 29 American Whites, 4 American Negroes and one of unknown race. The results indicate that regardless of race, sex, age, or tissue, in all cases the diploid chromosome number was 46.

Karyotype analyses have resulted in the identification of each individual human chromosome pair, including the sex pair. On the basis of relative chromosome lengths and arm indices, an idiogram of the human karyotype has been constructed in which each individual pair of chromosomes is designated by number. Statistical analysis has further established that homologous chromosomes from cells of the same or of different individuals do not differ significantly either in relative length or in centromere position. Similarly, there are no significant differences among X chromosomes or among Y chromosomes derived from different individuals.

To facilitate description and identification, human chromosomes have been grouped into 7 sub-groups. The morphological characteristics of chromosomes in each subgroup are described.

Two pairs of autosomes have satellites on their shorter arms. The presence of two pairs of nucleoli in somatic nuclei of both sexes supports the view that these pairs of satellited autosomes are nucleolus-organizing chromosomes.

ACKNOWLEDGMENTS

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ADDENDUM

Since the present manuscript was submitted for publication, a paper by Tjio and Puck describing their observations on the human karyotype has appeared (Proc. Nat. Acad. Sci. U. S. 44: 1229–1237, 1958). The results of the two studies are in substantial agreement as to cytological details, the principal difference being in the systems employed in numbering chromosomes.

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BOOK REVIEWS

The Evolution of Development

By J. T. Bonner. New York: Cambridge University Press, 1958, $3.50.

Developmental studies during the early part of this century were marked by a continuation of a trend which was popular in the last, namely a search for embryological evidences of evolutionary relationships. Now J. T. Bonner proposes, in his little book, that we may achieve a better insight into causation and epigenesis through an examination of the evolution of development itself. "... There has been, after all, an evolution of development along with the evolution of living organisms, and perhaps if we look at this aspect of development we shall see some of the problems of mechanism more clearly."

The book is divided into three lectures. The first deals with origins of development and stresses the evolution of development as a corollary to the trend towards size increase and the reproduction of organisms. The chief point made is that size increase usually involves multicellularity while reproductive mechanisms usually remain at the unicellular level. There is a discussion of the importance of the occurrence of variations and the mechanisms involved in their promulgation (cytoplasmic inheritence, diploidy, heterocaryosis, meiosis, etc.).

The keynote of the second lecture is that development leads to the elaboration of a co-ordinated individual and for this reason it is not surprising that there has been a selection of well co-ordinated developmental processes to achieve this end. A number of examples of developmental processes (including gene action, ciliate morphogenesis, mushroom development, etc.) are described. The importance of gradients, polarity and inductive phenomena is stressed. Finally the amoeboid slime molds and some aspects of their development and possible evolution are described in some detail.

Ideas about development are extended to associations of individuals in the last lecture. Essentially this is an account of behavior patterns and mechanisms involved in the establishment of societal relationships at various levels: between individuals (e.g. during mating), individuals to various objects and within groups.

Bonner writes in a rather facile and interesting style but, I am sorry to say, his book falls far short of being the exciting innovation that he seemed to intend. He touches very delicately on the important points—so lightly that there is some doubt that they have been made. Actually he has presented an account of different kinds of development at various levels of complexity and organization but leaves one with little more than a *feeling* that there is something here to be learned about the inter-relation of important mechanisms. This comes a bit too late to be an innovation; aside from its intrinsic interest the development of lower forms has been regarded by many people for a considerable time as a possible source of inspiration and analogy for the meaning of relationships observed in higher forms.

It is when he attempts to show the evolution of development of the systems which he describes in such a charming style that Bonner seems to be most weak. For instance, when he compares mosaic and regulative development, in effect he says that there must have been selective advantages to the elaboration of both types of development and these must somehow have evolved and their patterns have become fixed by inheritance. Obviously!

When he describes differentiation in slime molds as due to the establishment of discontinuous variations from previously continuous variations in the cell population he attempts to carry these ideas to the development of higher forms. Why he equates the cell variability

of the slime molds with the variable population of the egg's genes and cytoplasmic constituents baffles me. The user of an analogy may carry it where he wishes, but a comparison with the onset of variability in the cell population of a developing embryo seems more apropos to this reviewer.

This is a delightful little book despite the elusiveness of the main theme. I have reread it four times—at fairly widespread intervals—to be certain that I was not missing something. Possibly I have missed something important nevertheless, but, as far as the development of the announced objective of the book is concerned, I have the same feeling as did the little boy in the story about the emperor's new suit.

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Report of the United Nations Scientific Committee on the Effects of Atomic Radiation.

(GENERAL ASSEMBLY—OFFICIAL RECORDS: THIRTEENTH SESSION, Supplement No. 17 (A/3838).) Pp. iii + 228. New York: United Nations, 1958. $2.50.

PUBLIC INTEREST in the question of the biological effects of atomic radiation has forced the United Nations, through the medium of a special committee, to summarize relevant expert knowledge and publish it in the form of a report. The subject matter is not confined to atomic radiation but covers the whole field of ionizing rays and their effects. The matters reported upon are, first of all, the nature of radiation, its sources and its intensities in different circumstances. The pathological effects are, as usual, divided into the two classes, somatic and genetic. Finally, some general predictions and recommendations are outlined.

The report is the result of a prodigious amount of work on the part of the fifteen representatives who formed the official committee. Apart from these, seventy scientific experts are listed as having taken part in the preparation of the report. The attendance from different countries was curiously varied. As might be expected, most countries sent physicists or experts in radiology but those from Sweden and the United States were predominantly geneticists. In spite of this, only two members of the whole team could be classified as experts on human genetics although this topic occupies perhaps one third of the whole report. It is clear, however, that many other experts took part in the sense that they provided information, tables or references which influenced the committee. The number of references to scientific papers and the list of documents submitted on behalf of various countries represent an impressive quantity of data. There is no doubt that this report of the United Nations Scientific Committee on the Effects of Atomic Radiation is a most valuable compilation. For many years it is likely to be used as a standard source of information.

The parts of the report concerned with the physics of background radiation, atomic explosion fall out, isotopes and radiation biology, in Chapters II, III and IV, are clearly written. The presentation can be understood by anyone provided that the terminological mysteries of rads, roentgens, the RBE and the rem are mastered. There is much on which comment could be made here but I will only mention one striking problem. This arises in Chapter III where the relative amounts of radiation received from different sources are discussed. The doses are given in a form which is interpreted as equivalent to a genetically significant dose, that is one which reaches the gonads of a person likely to have offspring. On this basis it is calculated that the dose to germ cells from medical diagnostic exposures may be far greater than that from the natural background in countries which use X-rays

for such purposes. However, since it is stated that more than 80 per cent of this annual *per capita* gonad dose is contributed by six or seven special procedures, this hazard could easily be reduced by avoiding them in young subjects. In any case it is not clear to what part of the population these procedures are applied. The figure may be exaggerated because such procedures may be used mainly on unhealthy people whose expectation of offspring is less than average. In the report, the danger to future generations from irradiation for therapeutic purposes is considered negligible because it is not applied to potential parents.

Genetical questions first appear in the general chapter (Chapter II) when radiation injury is discussed. It is a pity that, in such an important document, dominance and recessivity are spoken of as properties of the genes rather than of the characters they determine. This can lead to a lot of confusion in human genetics. In Chapter V, where somatic effects on growing tissues such as skin, epiphyses and especially on bone marrow are discussed, genetical ideas are critical. The theory that tumour formation is caused by mutation is argued but no definite conclusions are stated. Estimates of the effects of radiation upon the future incidence of tumours are given on the assumption that 10 per cent of all primary bone tumours were caused by natural radiation and comparable calculations are made for leukaemia.

The section devoted to the genetical effects of radiation, which occupies Chapter VI, is the part which is most interesting for the purpose of this review. No one concerned with the subject would dispute the conclusions that research is needed in a wide variety of fields, both by observations on man and by experimentation on plants and animals, to improve our knowledge. The presentation of the knowledge and the ignorance which now exist in the human field is not always as clear as might have been hoped and there are many compromises evident. For example, a 'representative doubling dose' of 30 rad is accepted as a basis for calculating future trends. The idea of a representative doubling dose is a compromise derived from the British report to harmonize opposing views. Some authorities considered that, for practical purposes, all genes are equally sensitive to mutagenic action of radiation. A persistent minority objected to this, believing the work of Demerec, Westergaard, Fahmy and others to be relevant. However, the United Nations Committee reached the conclusion that 'mutations induced by ionizing radiations are in general similar in kind and effect to those of natural origin'. The operative phrase, 'similar in kind and effect', is not interpreted in human terms although parental age peculiarities of the skeletal mutations, as in achondroplasia, are mentioned.

The assumption that all human hereditary abnormalities can be lumped together, as is customary in counting lethals or 'visibles' in *Drosophila*, recurs frequently. In man there are many significant differences, such as age of onset and curability, which are absent when counting the cost of mutation in flies. The report estimates that 'about 4 per cent of liveborn infants suffer or will suffer from detectable genetic traits of importance'. What constitutes 'importance'? Presumably medical interest is one criterion because lists of autosomal and sex-linked diseases are given in the appendix and there have been heroic attempts to estimate phenotypical frequencies in all cases. The largest groups, as might be expected, fall in categories with uncertain genetical background. These are manic depressive reactions, diabetes mellitus, psoriasis, epilepsy, cataracts and exophthalmic goitre. The whole scheme seems to have been forced upon the committee simply because public opinion demanded that some estimate be made of the possible results of increasing the total dose of radiation to the human race. It would be a serious matter if superficial compilations of this sort were taken to indicate the modern standards of scientific work in human genetics. The question which the analysis seeks to answer is basically unsatisfactory. We cannot estimate how much disease is genetical in origin. All disease is genetical in origin to some extent. Moreover the concept used in the Report, of the social load produced by a given gene, is of very doubtful value.

And no definition is given. This load could perhaps theoretically be calculated in terms of expenditure of time and money in specific instances. The load is not proportional to lethality however; for example, anencephaly in some senses might be less burden than severe myopia. Nevertheless, the tables of genetical data provided in appendices will be useful and instructive to many people provided that their tentative nature is accepted. Some tabulations, such as that giving the DNA content of various types of cells and mutation rates in lower organisms, are both of intrinsic interest and convenient for comparative purposes.

There are several other obscurities in presentation of genetical data. What is the meaning of the term 'biometrical' applied to certain traits but not to others? Any biological trait can be made metrical if we choose to measure it and it would have been clearer to have used such terms as 'continuously varying', 'graded' or 'non-segregating' for the characters, like stature and intelligence, which are discussed. Birth weight is discussed extensively as an example of a biometrical trait in which extremes are unfavourable and there is much speculation about it in relation to mutation. Surely unfamiliar calculations and analyses, of the kind shown on pages 203 and 204, should have been published separately in scientific journals so that they could have been studied at leisure previously? The whole question of the selective significance of differences between optima and means in graded traits needs far more critical evaluation than is possible in a document such as this.

Conclusions about the likely effects of radiation received by the human population in future times are outlined in Chapter VII. In the case of fall out from nuclear weapon tests, wide limits are provided, as is prudent. Assumptions are made of minimal and maximal effects of radiation exposure both for leukaemia and for major genetic defects. For leukaemia, the operative question is whether or not small doses have any effect at all, and this is not yet known. For 'major genetic defects', among other doubts a large factor of uncertainty is the size of the 'doubling dose', which is assumed to lie between 10 and 100 rem. Accordingly, we may expect, if tests continue indefinitely, a number of extra cases, to look after every year, which will lie between 500 and 40,000 in the whole world. It is to be hoped that these figures will, for the time being, satisfy public opinion and that geneticists will be allowed to go on with their work upon facts instead of having to waste time in speculative argument.

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Bilateral Polycystic Disease of the Kidneys

By O. Z. DALGAARD. Copenhagen: E. Munksgaard, 1957, pp. 255.

THIS MONOGRAPH is an account of a remarkable collection of 242 cases of the adult form of bilateral polycystic kidney disease that was ascertained from various files of hospitals in greater Copenhagen for the period from 1920 through 1953. With this material in hand, the author spent approximately 2 years tracing the families (parents, siblings, children, siblings of parents, grandparents) of these affected individuals. There appeared to be 3445 family members in addition to the propositi. Information could be obtained from 1794 or 52 per cent of these relatives. No data could be found on any of the members of the families of 10 propositi so that this investigation was essentially limited to 232 affected individuals and half of their relatives. Seventy of 232 propositi, or 30 per cent, did not have relatives that were definitely affected, though the author suspected that 15 family members (among 13 propositi) could have had polycystic kidneys. Definite cases were discovered among 108 family members of 162 propositi, and furthermore 118 of the propositi were found to be related to one or more of the others. One family had 13 propositi and 9 other definite cases.

The author listed all of the propositi along with pertinent data on each of the affected family members, and he presented a few interesting pedigrees. Unfortunately, he did not indicate the size of each family nor the areas where information was lacking.

A large segment of the monograph was devoted to the clinical course of polycystic kidneys and the steps taken in making a diagnosis. Autopsy, operation, palpation of both kidneys and intravenous pyelograms were held to be the most essential techniques in making specific diagnoses. It was stressed that the diagnosis is often difficult since the malformation may not become apparent until middle age. Therefore, it may not be possible to be sure whether or not an individual is affected until he has lived almost his full life span. It is obvious that the effort involved in searching for information among family members and in personally examining living relatives was prodigious, but, as the author pointed out, there was no other way to conduct a thorough investigation.

There is a great deal of statistical treatment of the data, but at times the author's purposes are not clear. For example, in Chapter 2, he sets forth the age specific incidence and the morbid risk of polycystic kidneys in the general population. He includes a good discussion of the possible biases and shortcomings of his data, but he computes standard errors valid only for large random samples. He apparently does not consider the standard errors when he states "... the morbid risk curves for the time before 1935 lie considerably lower than the curves after 1935", because, for neither sex, is the difference at any age close to two standard errors of the difference. (In Figures 1 and 2, the difference between the curves looks impressive, but this is mainly because the author has graphed unadjusted intermediate figures rather than the morbid risks of Table 3.)

One chapter is devoted to a discussion of associated malformations, particularly polycystic liver, which, in this survey, seems to have had an etiologic connection with polycystic kidneys. The author was less certain that aneurysm of the basal artery was strictly related to the renal malformation. In addition, 40 cases of congenital polycystic disease of the kidneys were uncovered. These cases were analysed on the assumption that they are etiologically different from the adult form.

In summary, this is an unusual treatise on a subject of genetic import, and certainly one of the most extensive studies of the clinical and hereditary nature of this disorder.

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The Genetic Basis of Selection

By I. MICHAEL LERNER. New York: John Wiley and Sons (London: Chapman and Hall), 1958, pp. 298, $8.00.

THE GENETIC BASIS OF SELECTION is written by an outstanding geneticist and an authority in poultry breeding. Anticipating readers from other fields, the author states in the *Preface*: "The reader need not know much about poultry. . . . But I hope that when he has finished it, he will . . . be able to apply freely the principles discussed here to the species of his own interest." The reviewer and the majority of the readers of this *Journal* fall into this class, and here, of course, the species of our interest is man. Although experiments on selection in Drosophila and mice have also been cited, the author mentions man explicitly only once (p. 165) and that is when he discusses the effects of common environment (the C effects) for siblings. But the reader will not be disappointed. Unable to do full justice to the book because of ignorance of poultry breeding problems, I can say, however, without hesitation

that the book will prove highly profitable reading even for those primarily interested in human genetics. He will learn a great deal about genetics in general and selection genetics in particular. He will be exposed to some very fundamental concepts in modern population genetics (such as the coadapted system of a gene pool) and a wide range of considerations should a certain type of selection pressure be contemplated. The vast body of knowledge accumulated from selection experiments on animals makes some discussions and speculations on the consequences of selection in man sound naive. Wholesale genetic changes simply do not occur in as simple a manner as we would like to think.

Obviously, application of the findings in poultry to man requires caution and the responsibility rests with the human geneticist. For instance, the poultry breeder finds that the weight of eggs has a much higher heritability than the number of eggs laid in a certain period of the year (p. 62 and several other places). In this case, the application to man is at best very remote. On the other hand, it has been found that "crooked" toes in chickens, and many other characteristics in other animals, are conditioned by small differences at a large number of loci with threshold for expression. When a certain fraction of these loci is homozygous, the trait is phenotypically expressed and classifiable into discrete categories. Inbreeding increases the incidence of the trait sharply. Selection by culling the individuals exhibiting the trait is virtually ineffective. If a somewhat similar physical abnormality occurs in man, most human geneticists would tend to think that it is a simple mendelian recessive. The truth is that for such *phenodeviants* "no formal mendelian schemes can be usefully invoked even when variable penetrance and expressivity of single genes is postulated" (p. 68).

Selection with respect to one trait usually leads to changes in other traits for which there has been no selection intended. The problem of "correlated response" to selection is discussed in several places in the book (p. 144, etc.). One of the most serious collateral changes is lower viability or lower fertility. Indeed, reproductive capacity may become so low that, in order to save the breeding stock from extinction, selection must be suspended temporarily. Such a phenomenon occurs in mice, flies, as well as in poultry. No clear-cut or satisfactory explanation for this is in order although linkage in the polygenic systems organized in blocks (segments of chromosomes) and small size of the experimental population have been suggested to be partially responsible.

Continued selection also leads to a plateau of the trait. After a certain level is reached further selection becomes ineffective. Simple genetic considerations suggest that the population is fixed with respect to the loci controlling the trait. Much evidence, however, shows that this is usually not the case. For example, a plateaued trait may respond to reverse selection (p. 121) showing that the population is not in a completely homozygous state. Again, the explanation for this phenomenon is far from final. Many selection experiments on various characters are still going on both sides of the Atlantic.

Selection for most practical purposes is based not on any single merit but on a constellation of desirable traits. Selection with multiple objectives, when possible, lowers the selection intensity for each separate trait (p. 176). When desirable traits are negatively correlated, the selection task will be doubly difficult. On the other hand, selection of exceedingly high intensity (e.g. one in a thousand or a million) may result in genetic regression instead of improvement because the one chosen may be an unbuffered individual with poor genotype and a predisposition to vary with the environment (p. 122). Also, "there is little that selection theory can offer a breeder to help him satisfy an ambition to produce a single champion performer. Counsel to practice somatic assortment by mating the best to the best would be as useful as carrying coals to Newcastle, especially if the method of ascertainment of what is the best is left unspecified" (p. 110).

The situations described in the preceding paragraphs are by no means limited to poultry

but are quite common in all experimental populations. The few points brought out above are sufficient to remind us how little is known of the possible consequences of artificial selection in man and make us think twice before outlining a "positive" program for the improvement of mankind. The author discusses, not as pointedly as did Professor K. Mather, the difference between the slow all-embracing natural selection which allows the gradual reorganization of a coadaptive system in the gene pool and the drastic short-term artificial selection which destroys such a system.

The reader will also learn a great deal about some general principles in population genetics. A few examples follow. Equilibrium depends on the balance of disturbing factors rather than their absence (p. 73). Epistasis alone cannot maintain genetic polymorphism (p. 75). Overdominance is no aid to directional selection within a population (p. 96). Genetic improvement is a slow process; reversion often occurs upon suspension of selection (pp. 194–195). But the reversion to the original phenotype may involve a different gene pool content (p. 128). The general issue of breeding for heterosis falls more into the area of mating systems than that of selection (p. 223). Various diseases may interfere with selection advance (p. 203). Changes of environment lead to redefinition of fitness and to shifts of emphasis from one factor to another (p. 239). If the reader is familiar with the statistical definition of the additive component of genetic variance and heritability, he will appreciate the author's discussions that much more. If the non-additive variability and the genotype-environment interaction can mislead an experienced breeder in a poultry farm, the task of predicting the consequences of selection in man is undoubtedly insurmountable.

As to the outlook of selection in poultry, it is questionable how successfully the genetic methods of stock improvement can compete with non-genetic techniques (medicine, nutrition, etc.) for increasing agricultural production, which are being discovered in profusion day by day (p. 224). To meet this challenge, the author outlines a number of bold and daring possible undertakings by which the breeder may obtain new kinds of animals (p. 268 ff).

Some defects and lapses of the book may be noted. In most of the figures illustrating a theoretical relationship, the equation of the plotted curve is not given. (The curve representing an equation should be distinguished from the diagrams showing observed results. For the latter, no explicit expression is necessary.) Some of the numerical examples in the "Boxes" (separate inserts) are so much over-simplified that certain general properties of the situation are lost. In most of the path diagrams there is one or more redundant double arrowheaded correlation line so that the diagrams look more complicated than they really are. These redundant lines might have been deleted from the diagram or shown by dotted lines merely serving to fix attention. In conclusion, I would agree with the book's title that this is a book on selection genetics rather than on poultry breeding.

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"Genetics, A Survey of the Principles of Heredity"

By A. M. Winchester. Second Edition. Boston: Houghton Mifflin Company, 1958, 414 pages, $6.25.

Professor Winchester has incorporated into this second edition some of the important developments since the 1951 edition. A short, but useful and thought-provoking chapter is devoted to the "survival of man in an atomic age"; included in this chapter are discussions of sources of radiation, somatic and genetic radiation damage, and the recommendations of American and British groups to reduce radiation hazards. A chapter on microbial genetics provides some of the highlights of transformation in pneumococcus, recombination and

transduction in *E. coli*, and brief mention of plaque mutants of phage T2. A chapter on the nature of genes includes evidence from bacterial and viral studies supporting the view that DNA is the genetic material, and mention of the recent attempts to synthesize DNA.

The treatment of the core of genetic principles is generally simplified with a deliberate avoidance of mathematical as well as genetic symbolism. This treatment is probably too successful to satisfy students who are reasonably proficient in high school algebra. The needs of inquiring students (whether or not they intend to make further studies of genetics) are frustrated by the omission of additional references to specific topics, although a list of 30 additional books is provided without comment at the end of the book. The phrasing and reasoning are frequently questionable or confusing, and the dogmatic or naive treatment of some topics leads to misinterpretations or to statements not commensurate with the reliability of the evidence. The unsophisticated student is not likely to be bothered by such a treatment, but the student with ability and interest might find himself fighting genetics rather than enjoying it.

The avoidance of symbolism is well illustrated by the chapter on linked genes and chromosome mapping which is written without once using symbols for genotypes. The chapter on probability omits mention of mutually exclusive events, although the treatment of independent events is well done. Yet the adequately developed "fraction method" (page 147) is never applied to determining the results of multi-hybrid crosses where its advantage over the tedious checkerboard is obvious.

Space limitations permit only illustrations of the most frequent types of sins of commission:

Without mention of the dubious nature of the evidence, the chapter on linkage includes a map of seven partially sex-linked human genes, and maps of five human autosomes including 18 loci (pages 198–201). Strangely, the two better established autosomal linkages published in time to be included in the text (elliptocytosis with the Rh antigens, and the nail-patella syndrome with the ABO antigens) are not mentioned.

The directness of inheritance of certain traits leads to the statement (page 180) that "the A antigen is produced by the gene I^A only; it needs no assistance from genes at other loci. Likewise, a single gene seems to be the sole factor responsible for each of a number of important cellular enzymes".

The reason given for the practice of double-cross hybridization in corn is wrong (page 350).

Professor Winchester implies (page 228) that it is probably incorrect to consider the gene as "part of a continuous chain of genetic material" and should more properly be considered "a discrete unit of the chromosome". Yet his own discussion of genic fine structure (page 234) makes it apparent that the units of recombination, mutation, and function must be overlapping to some extent.

Confusion is illustrated by the discussion of the balance concept of sex determination where it is not clear what ratio is meant in this statement (page 98): "The fly receiving the three X-chromosomes is a so-called 'superfemale,' for the ratio here is 4.5 for femaleness and 2 for maleness, which is greater than the 3:2 ratio characteristic of normal females." (Instead of using directly the *numbers* of X-chromosomes and autosomal genomes, he assigns to an X-chromosome a female-stimulating strength of 1.5 and to an autosomal genome a male-stimulating strength of 1.0, so that a "femaleness to maleness" ratio of 1.0 is an intersex.)

There is also confusion with regard to Paramecium's paramecin which is considered both a protozoan antibiotic and a particle (page 311), and with regard to the "honeybee method" where the word "infertile" is used to mean "unfertilized" (pages 101 and 102).

Phraseology is often strange. For example:

"In his own words, as translated from the Russian . . ." (page 8).

"When we study two alleles for different expressions of a characteristic . . . we usually find that one of the two genes has greater strength than the other and dominates it." (page 70).

"Genes for stamens and genes for pistils express themselves at the proper time and place just as the genes for leaves, roots, bark, and other parts of the plant express themselves at the proper time and place." (page 90).

"The gaseous emanation from radium gives off the rays just as radium does, but the amount of rays given off by the gas diminishes with time, and it is necessary to have accurate knowledge of the age of the emanation to estimate this." (page 271).

It is, of course, desirable and proper to disseminate knowledge of genetics to initially uninterested students or to interested students unable to grasp a more symbolic treatment than Winchester's book affords. A simplified approach with a gradual sneaking up on general principles through the use of specific examples (for instance, Winchester's treatment of chi-square) is fully justifiable, and for classes composed largely of such students this book might be approrpiate. Interest in genetics is created and maintained primarily by stressing human heredity. A multitude of photographs illustrate human abnormalities (including before and after views of C. Jorgensen). The use of anecdotes is generally effective, and the chapter on eugenics—always of interest to students—is well written. With few exceptions the line drawings are interesting and remarkably graphic, and the book as a whole is esthetically pleasing. The problems at the end of each chapter are generally thought-provoking, and often require deductions from textural material.

However, it is questionable whether these admirable characteristics compensate for a text which is frequently confusing, misleading, or incorrect.

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Variables Related To Human Breast Cancer

By V. E. ANDERSON, H. O. GOODMAN, AND S. C. REED. Minneapolis: University of Minnesota Press, $4.00.

THIS VOLUME is a report of a study designed to answer the question, "Do relatives of breast cancer patients have an increased risk of developing cancer?" The 544 propositae selected for study were women who were examined at the Tumor Clinic of the University of Minnesota Hospitals during the period 1931–1952, and who had a microscopic diagnosis of breast carcinoma or who (in 17 cases) had clinically diagnosed inoperable breast cancer. The control group (for comparison with the blood relatives) was composed of the parents and siblings of the husbands of the propositae.

Data are presented to indicate that the propositae were not a representative sample of breast cancer patients in the state of Minnesota. More of the propositae came from rural areas and from lower economic groups of the population than would be expected on a chance basis. However, the authors felt that the control group was sufficiently comparable to the propositae that a valid answer to the question could be obtained.

Information concerning relatives was obtained through interviews and letters. Attempts were made to secure copies of death certificates for relatives who died in the United States or Canada. Medical history questionnaires were sent to living relatives and to physicians and hospitals to verify reported cancers and tumors.

It is of interest that complete information was received for a higher proportion of relatives of the cancer group (88%) than of the control group (80%) and that more of the cancers

of the cancer group were verified by microscopic diagnosis. Analyses were limited to relatives with reports and to cases of cancer verified by microscopic diagnosis, death record, clinical examination, x-ray, or surgery.

For evaluation of the frequency of cancer among relatives, several methods of statistical analyses were employed, as follows: 1) comparison of observed number of cancers among deceased relatives with the number expected on the basis of proportionate mortality ratios calculated from deaths in Minnesota for the years 1910–1949. 2) Comparisons of the observed number of cancers among both living and dead relatives with the number expected on the basis of mortality and morbidity rates. To obtain the expected numbers three types of data were used resulting in three comparisons; the data used were, (a) Iowa cancer morbidity rates for 1900, (b) Minnesota cancer mortality rates for 1939–1941 and (c) proportionate mortality ratios from Minnesota for the dead relatives and both morbidity and mortality rates for living relatives. In this instance, the expected number using mortality rates was subtracted from the number using morbidity rates to provide an approximation to the number of individuals developing cancer but not dying from it. It is of more than passing interest that these three types of comparisons resulted in different expected numbers. 3) Comparison of cancer and control groups by means of (a) age-adjusted frequencies, (b) morbid risks using the method of Böök and, (c) sequential analysis as proposed by Macklin.

With the exception of the sequential analysis all of the above comparisons showed about 1.8 times as much breast cancer among sisters of the breast cancer patients as among sisters of the controls. Mothers of propositae showed a similar excess of breast cancer only if unverified cases were included.

These data did not provide a good estimate of the breast cancer risk for daughters of the propositae. A second set of propositae was selected from a group of women with breast cancer diagnosed between 1910 and 1925 and information was obtained concerning their married daughters and the son's wives. The married daughters had about three times the expected number of breast cancers.

The authors' interpretation of these results is quite conservative. They felt that "it is very likely that genetic factors were involved in the etiology of breast cancer". However, "the differences are not large enough to permit a definite conclusion by itself but in conjunction with other investigations, the consistency of the excess indicates that it is real, even though small". They indicate the need for further research on this problem and list several specific lines of investigation that are suggested by the results of this study.

To this reviewer, the most significant aspect of this book lies not in the specific study reported but in the critical discussion of the advantages and disadvantages of various methods of analysis used in such studies, in the review and evaluation of the previous studies carried out in this area and in the presentation of the methodological problems that are met in human genetic studies. For these reasons, this report should be read by both human geneticists and epidemiologists who are concerned with genetic aspects of human disease.

It is clear from the results of this study and from other similar studies that the evidence of inheritance of breast cancer can be regarded at the most, as being suggestive. There still exists the need for a coordinated genetic and epidemiological study of a representative sample of breast cancer patients in a community. In view of the unsettled question as to the best type of control to be used, perhaps it would be best to have several types of controls, such as, a probability sample of the female population of a community, the relatives of the spouse of the patient as in the present study, and patients with other types of cancer. Such a study would overcome many of the methodological problems encountered in the present study.

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Über die Erblichkeit des normalen Elektroenzephalogramms

By F. VOGEL. Stuttgart: Georg Thieme Verlag, 1958, 92 pp., 25 tables.

WITH COMPARATIVE EEG records of 208 pairs of twins, 110 monozygotic and 98 dizygotic, this penetrating report represents one of the most extensive electroencephalographic studies of normal twins to date. Simultaneous tracings of each pair were recorded on a 16-channel machine under the following conditions: normal waking state, natural sleep, and under the "stress" of mental activity and induced states of mild alkalosis and hypoxia. The modern similarity method was used in determining zygosity, and included haematologic and dermatoglyphic comparison as well as PTC and secretor factor tests.

As to the basic characteristics of brain wave patterns, intra-pair similarity was observed in all MZ and about one-third (39%) of DZ pairs. Mean amplitude values were obtained with a specially designed instrument called a "planimeter" and also proved to be extremely similar in one-egg twins, and clearly dissimilar in two-egg twins. Moreover, it was found only in MZ pairs that the alpha index differences between twin partners did not exceed intra-person variations, while a newly devised sub-alpha index (brain waves of 133.3 sigma and more, in per cent) seemed to vary more extensively with age than between the two zygosity groups. Perhaps the most striking feature of the study was the fact that the investigator was able, from a 30 cm. strip of EEG, to identify monozygosity correctly in 83 per cent of his series on the first attempt, and in a total of 96 per cent in the second round.

In a group of twins with records of predominantly fast activity, intra-pair similarity was established in 100 per cent of MZ pairs and 55 per cent of DZ pairs. The responses to both "stressful" states and various sleep levels confirmed the tendency of one-egg twins to be much more similar in their records than was seen in the two-egg group. However, no evidence was obtained either of intra-pair specularity with respect to alpha index and amplitude values (reversed asymmetry) or of any relationship between quantitative EEG measurements and handedness variations. The statistical techniques employed throughout the study left nothing to be desired, although an analysis of variance might have been of interest.

Regarding the single-factor theory of dysrhythmia and its relationship to convulsive disease, the author maintains admirable restraint. Since he considers all available data as inconclusive at the present state of knowledge, he emphasizes the need for a better understanding of the genetic aspects of "normal" EEG responses and deserves much credit for his careful research in this complex area. Altogether, this monograph is an excellent and methodologically valuable contribution to modern medical genetics.

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LETTERS TO THE EDITOR

Tyrosinase and Albinism

October 6, 1958

To the Editor
Dear Sir:

I wish to make two comments concerning the article entitled "Sir Archibald Garrod's 'Inborn Errors of Metabolism' III. Albinism" by W. Eugene Knox in the September, 1958 issue of this Journal.

The first concerns the postulation, by a large number of writers on the subject of albinism, that tyrosinase is one of the possible defective enzymes in the metabolic pathway for the formation of melanin. Tyrosinase is currently postulated as an enzyme necessary in the formation of epinephrine. If this is true, one would expect to find a defect in the production of this substance in albinos. The catacholamine determinations that we have performed on a considerable number of patients with total albinism, have failed to show any significant deviations from normal. The possibility that there are alternate pathways for epinephrine synthesis that do not include tyrosinase, has been posulated from some recent work; so that lack of tyrosinase may be the enzyme defect of choice in albinism at present, but with some reservation as to its role in epinephrine synthesis.

The second comment is a minor one concerning an earlier reference to malignant amelanotic melanoma occurring in complete albinos (Bhender, Y. M.: Malignant Amelanotic Melanoma of Skin in Albino. Indian J. M. Sc. *6:* 755–759, Nov., 1952).

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Abinism: Reply to Dr. Witkop

Oct. 27, 1958

To the Editor
Dear Sir:

It is unpopular to conclude that our knowledge is less secure than is generally thought, and so I particularly welcome Dr. Witkop's support of my position on human albinism. Separate compartmentalization of the reactions of tyrosine to dopa to pigment, and of tyrosine to dopa to epinephrine, could account for a normal epinephrine formation in albinos. But I would prefer for the present to let these ingenious and original experiments emphasize how insecure is the postulation of defective tyrosinase in albinism. From available evidence (in man) I could only conclude that "a variety of abnormalities (in the subcellular particles of the melanocytes) could account for the inability to form pigment, and one of these possibilities is the absence or ineffectiveness of the tyrosinase."

That the defect is subcellular rests on the evidence that (amelanotic) melanocytes are present in the human albino. The second instance of an amelanotic melanoma in an albino is therefore especially important, since the two known tumors now constitute the only good evidence on this point. The dendritic cells revealed by gold-impregnation studies in the human albino skin, which I accepted as melanocytes, may not be these cells. W. K. Silvers has recently shown that the cells demonstrable by the same technique in guinea pig and mouse skins have no relation to melanocytes. But he has also proved by genetic and transplantation techniques that the "clear cells" in the hair bulbs of albino mice are amelanotic melanocytes (Am. J. Anat. *100*, 225–240 (1957); Anat. Rec. *130*, 135–144 (1958).

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Fertility Differential in Two Lappish Populations

October 6, 1958

To the Editor
Dear Sir:

At a recent Wenner-Gren Supper Conference on natural selection in man (1) J. V. Neel emphasized the need for a variety of parallel studies on selective factors in advanced and primitive societies. Among such selective factors the variability in individual reproductive performances has certainly important evolutionary implications. At the same Conference J. F. Crow proposed a simple test for the estimation of the components of selection due to differential fertility and mortality.

In Table 1 (p. 47) of his paper Neel collects some figures on the reproductive performance of mothers in "primitive" populations. I find it of some interest to supplement his Table with similar data from two populations of Swedish Lapps, one nomadic and one settled, leading different lives in a geographically similar environment. The figures set out in the accompanying table are extracted from the monograph of S. Wahlund (2). Life in Northern Lappland in the period to which the figures refer must have been rough. Whether the conditions could also be called "primitive" is another question. If the concept of primitive goes together with lack of vital statistics, the very fact that such good statistics are available for these populations would discourage any temptation to call them primitive.

TABLE 1. NUMBER OF CHILDREN EVER BORN (LIVE- AND STILLBORN) TO WOMEN AGED 45 YEARS AND OVER IN TWO LAPPISH POPULATIONS. THE FIGURES REFER TO THE PERIOD 1791–1890

No. of children	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	Total
No. of mothers																			
Nomad . .	75	53	52	59	43	55	77	56	67	36	34	13	14	2	3	—	—	—	639
Settled . . .	98	38	46	76	64	91	96	101	97	78	65	46	20	16	7	4	2	1	946

As seen from the table, the sterility rate, i.e. the proportion of women who did not bear children is high, being higher, but not significantly so in the nomadic than in the settled Lapps (11.7 versus 10.4 per cent). These rates of sterility compare with those from New South Wales (10.8 per cent and Liberia (11.9 her cent) in Neel's table. It is of interest to note that Böök (3) has observed one sterile marriage out of 30 marriages with completed period of fertility, in a small isolate population in North Sweden. Among the figures quoted by Neel only that found by Malaurie et al (4) in a small sample of Greenland Eskimos (15.7 per cent) is higher than the present ones.

Differences in individual fertilities are striking. In the nomadic population women having six or more children are 47 per cent of the total and contribute 76 per cent of the total number of children. The proportions are 56 and 81 per cent, respectively, in the settled population.

As Neel says, the implications of these differentials for natural selection depend on the degree to which they are genetically determined. The facts discussed above would seem to endorse fully the contention that research on selective factors in different types of human societies is imperative.

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